Unified Patent Court
Einheitliches Patentgericht
Juridiction unifiée du brevet

UPC Court of Appeal
UPC_CoA_528/2024
UPC_CoA_529/2024

DECISION

of the Court of Appeal of the Unified Patent Court
issued on 25 November 2025
concerning appeals in a revocation action and a counterclaim for revocation

HEADNOTES

Claim interpretation

1. The question of whether conclusions can be drawn from the subject matter of a dependent claim and its features when interpreting the main claim depends on the circumstances of the individual case. If the dependent claim is only adding an additional feature that does not provide a more specific description of the features of the main claim, it generally argues against the possibility of drawing conclusions about the interpretation of the main claim from this dependent claim.

2. When the claims are drafted in 'medical use-format', it is an inherent claim feature that the claimed product must be objectively suitable for the claimed use, i.e. be therapeutically effective. This requires that the claimed treatment causes a noticeable improvement of the medical condition of the patient suffering from the disease mentioned in the claim, i.e. the treatment must be meaningful.

3. The fact that the skilled person does not derive any minimum required effect from the claim or the description does not lead to another conclusion, since the feature of therapeutic effect does not follow from the claim language that is to be interpreted, but from the use of the medical use claim format.

Added matter

4. The assessment of whether there is added matter is a question of law to be decided on the basis of the facts brought forward by the parties. The facts are the relevant claims and the application as filed. Since the test is whether the relevant claims have basis in the application *as a whole*, the Court is allowed to look at the entire document.

Sufficiency

5. Sufficiency has to be examined on the basis of the patent as a whole, thus on the basis of the claims, description and drawings, from the perspective of the skilled person with his common general knowledge at the filing or priority date.

6. The test to be applied is whether the skilled person is able to reproduce the claimed subject matter on the basis of the patent without any inventive effort and without undue burden. An invention is sufficiently disclosed if the patent specification shows the skilled person at least one way – and in case of functional features: one technical concept – of performing the claimed invention.

7. Where a claim contains one or more functional features, it is not required that the disclosure includes specific instructions as to how each and every conceivable embodiment within the functional definition(s) should be obtained. A fair protection requires that variants of specifically disclosed embodiments that are equally suitable to achieve the same effect, which could not have been envisaged without the invention, should also be protected by the claim. Consequently, any non-availability of some embodiments of a functionally defined claim is immaterial to sufficiency, as long as the skilled person through the disclosure is able to obtain suitable embodiments within the scope of the claim.

8. A reasonable amount of trial and error does not prevent the invention from being enabled.

9. The burden of presentation and proof lies with the party invoking invalidity of the patent.

Inventive step

10. The approach taken by the Unified Patent Court when establishing inventive step is as follows.

11. It first has to be established what the object of the invention is, i.e. the objective problem. This must be assessed from the perspective of the skilled person (m/f – hereinafter referred to as 'it'), with its common general knowledge, as at the application or priority date (also referred to as the relevant date) of the patent. This must be done by establishing what the invention adds to the state of the art, not by looking at the individual features of the claim, but by comparing the claim as a whole in context of the description and the drawings, thus also considering the inventive concept underlying the invention (the technical teaching), which must be based on the technical effect(s) that the skilled person on the basis of the application understands is (are) achieved with the claimed invention.

12. In order to avoid hindsight, the objective problem should not contain pointers to the claimed solution.

13. The claimed solution is obvious when at the relevant date the skilled person, starting from a realistic starting point in the state of the art in the relevant field of technology, wishing to solve the objective problem, *would* (and not only: *could*) have arrived at the claimed solution.

14. The relevant field of technology is the field relevant to the objective problem to be solved as well as any field in which the same or similar problem arises and of which the person skilled in the art of the specific field must be expected to be aware.

15. A starting point is realistic if the teaching thereof would have been of interest to a skilled person who, at the relevant date, wishes to solve the objective problem. This may for instance be the case if the relevant piece of prior art already discloses several features similar to those relevant to the invention as claimed and/or addresses the same or a similar underlying problem as that of the claimed invention. There can be more than one realistic starting point and the claimed invention must be inventive starting from each of them.

16. The skilled person has no inventive skills and no imagination and requires a pointer or motivation that, starting from a realistic starting point, directs it to implement a next step in the direction of the claimed invention. As a general rule, a claimed solution must be considered not inventive / obvious when the skilled person *would* take the next step prompted by the pointer or as a matter of routine, and arrive at the claimed invention.

17. A claimed solution is obvious if the skilled person would have taken the next step in expectation of finding an envisaged solution of his technical problem. This is generally the case when the results of the next step were clearly predictable, or where there was a reasonable expectation of success.

18. The burden of proof that the results were clearly predictable or the skilled person would have reasonably expected success, i.e. that the solution he envisages by taking the next step would solve the objective problem, lies on the party asserting invalidity of the patent.

19. A reasonable expectation of success implies the ability of the skilled person to predict rationally, on the basis of scientific appraisal of the known facts before a research project was started, the successful conclusion of that project within acceptable time limits.

20. Whether there is a reasonable expectation of success depends on the circumstances of the case. The more unexplored a technical field of research, the more difficult it was to make predictions about its successful conclusion and the lower the expectation of success. Envisaged practical or technical difficulties as well as the costs involved in testing whether the desired result will be obtained when taking a next step may also withhold the skilled person from taking that step. On the other hand, the stronger a pointer towards the claimed solution, the lower the threshold for a reasonable expectation of success.

21. When the patentee brings forward and sufficiently substantiates uncertainties and / or practical or technical difficulties, the burden of proof that these would not prevent a skilled person from having a reasonable expectation of success, falls on the party alleging obviousness.

22. The fact that other persons or teams were working contemporaneously on the same project does not necessarily imply that there was a reasonable expectation of success. It may also indicate that it was an interesting area to explore with a mere hope to succeed.

KEYWORDS

claim interpretation medical use claim; added matter; sufficiency; inventive step; reasonable expectation of success

APPELLANT (AND DEFENDANT BEFORE THE COURT OF FIRST INSTANCE)

AMGEN, INC, Thousand Oaks, USA (hereinafter referred to as "Amgen")

represented by Koen Bijvank, attorney-at-law, Brinkhof N.V., Amsterdam, The Netherlands and representatives from Bardehle Pagenberg, Munich, Germany

RESPONDENTS (AND CLAIMANTS AND COUNTER-CLAIMANT RESPECTIVELY BEFORE THE COURT OF FIRST INSTANCE)

1. **SANOFI-AVENTIS DEUTSCHLAND GMBH**, Frankfurt am Main, Germany
2. **SANOFI-AVENTIS GROUPE S.A.,** Gentilly, France
3. **SANOFI WINTHROP INDUSTRIE S.A.**, Gentilly, France

(hereinafter jointly referred to as "Sanofi")

all represented by Daniel Wise, attorney-at-law, Carpmaels & Ransford, London, The United Kingdom and other representatives from that law firm

and

Regeneron Pharmaceuticals Inc., Rensselaer, USA
(hereinafter referred to as "Regeneron" and together with Sanofi as "Respondents").

represented by Niels Hölder, attorney-at-law, Hoffmann Eitle, Munich, Germany as well as Daniel Wise, attorney-at-law, Carpmaels & Ransford, London, United Kingdom, and other representatives from that law firm.

LANGUAGE OF THE PROCEEDINGS

English

PATENT AT ISSUE

EP 3 666 797

PANEL AND DECIDING JUDGES

This decision was issued by panel 2:
Rian Kalden, presiding judge and judge-rapporteur
Patricia Rombach, legally qualified judge
Ingeborg Simonsson, legally qualified judge
Rainer Friedrich, technically qualified judge
Cornelis Schüller, technically qualified judge

IMPUGNED DECISIONS OF THE COURT OF FIRST INSTANCE

The decision in UPC_CFI_1/2023 concerning a revocation action, the decision in UPC_CFI_14/2023 concerning a counterclaim for revocation, both issued by the Munich central division on 16 July 2024.

ORAL HEARING
12 August 2025

SUMMARY OF THE FACTS

The parties

1. Amgen and the Respondents market cholesterol-lowering antibody drugs which are biotechnologically produced PCSK9 inhibitors. Amgen's drug is sold under the trade name Repatha®. The Respondents sell a cholesterol-lowering drug under the trade name Praluent®.

The patent at issue

2. Amgen is the registered owner of the patent entitled "ANTIGEN BINDING PROTEINS TO PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)" which was filed on 22 August 2008 (application as filed WO 2009/026558, Exh. A1). The patent derives from a European (multigenerational) divisional patent application (EP 19207796.4). The application is ultimately derived from PCT application PCT/US2008/074097, which was filed on 22 August 2008, published as WO2009/026558 (A1), and entered the European regional phase as EP Application No. 08798550.3 (granted as EP 2 215 124).

3. The patent claims priority to US20070957668P (P1, 23.08.2007), US20070008965P (P2, 21.12.2007), US20080010630P (P3, 09.01.2008) and US20080086133 (P4, 04.08.2008).

4. The publication of the mention of the grant of the patent was made on 17 May 2023.

5. The patent is in force in the UPC Contracting Member States Austria, Belgium, Bulgaria, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Portugal, Slovenia and Sweden (hereinafter: the Territories).

6. The patent has one independent claim and ten dependent claims (claims 2-11). Claim 1 of the patent as granted reads:

> *A monoclonal antibody or an antigen-binding fragment thereof for use in*
> *treating or preventing hypercholesterolemia or an atherosclerotic disease related to elevated serum cholesterol levels;*

or for use in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels;
wherein the monoclonal antibody or the antigen-binding fragment thereof binds to the catalytic domain of a PCSK9 protein of the amino acid sequence of SEQ ID NO: 1, and prevents or reduces the binding of PCSK9 to LDLR.

Opposition proceedings before the EPO

7. Opposition against the grant of the patent at the European Patent Office ("EPO") was lodged by Sanofi-Aventis Deutschland GmbH on 10 November 2023 and by Regeneron Pharmaceuticals Inc. on 19 February 2024.

8. By decision of 21 May 2025 the Opposition Division rejected the opposition and upheld the patent as granted. An appeal from this decision is presently pending before the Technical Board of Appeal.

Technical background

9. The technical introduction provided in the impugned decision has not been objected to and will be repeated below.

10. An antibody is a type of protein (also called an immunoglobulin, "Ig") that is produced by the immune system in response to a foreign substance. Each antibody recognizes a particular target, also referred to as an "antigen". Like all proteins, antibodies are made up of amino acids. Each amino acid has distinct chemical and physical properties. The amino acid sequence of an antibody is a major factor affecting how the antibody protein will fold into a three-dimensional structure, which in turn helps to determine which antigen or antigens the protein can bind, and how the antibody functions.

11. Each antibody is made up of two pairs of identical polypeptide chains (chains of amino acids linked together by peptide bonds) that form a flexible Y shape. Each pair comprises a heavy chain polypeptide (the green segments depicted in the figure below) and a light chain polypeptide (the blue segments depicted in the figure below) that are held together by disulfide bonds ("-SS-" in the figure). Each polypeptide chain, light or heavy, has a "constant" and a "variable" domain. The ordering of amino acids in the heavy and light chain protein sequences of an antibody is encoded by the heavy and light chain genes for that antibody.

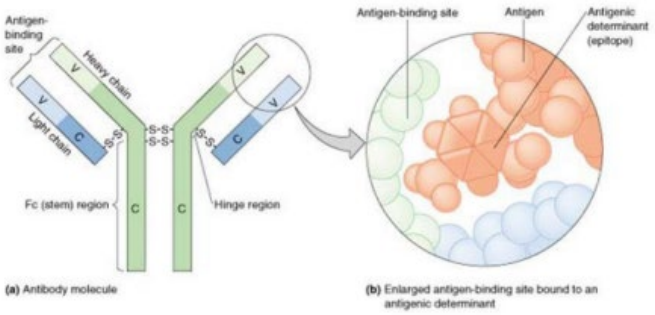


Figure 4 in the CC.

12. The variable domains are referred to as such because the amino acid sequence in these domains differs between antibodies. The variable domains make up the antigen-binding sites of an antibody, with each of the two antigen-binding sites within a particular antibody being identical.

13. The epitope is the region of an antigen that is bound by an antibody. When the antigen is a protein, the binding of an antibody to its antigen occurs via interactions between the amino acid residues on the antibody and the amino acid residues on the antigen.

14. As of the earliest priority date of the patent in 2007, methods of making antibodies were well-established.

15. For example, antibodies can be made by immunizing mice. That involves immunizing mice with the desired target antigen, harvesting the mice, collecting the antibody-producing mouse B cells and fusing them with "immortal" cells to create "hybridomas." Antibodies generated by the mouse immune system are then collected from the hybridomas for screening, each hybridoma cell producing a single antibody.

16. Alternatively, a method called phage display could be used in which an antibody sequence is presented on the surface of a bacteriophage. By repeating this process, one is able to produce many millions of bacteriophages each presenting a different antibody variable region that form a "library." This library can then be screened for binding to a target antigen of interest. Other display techniques were also available. For example, yeast display is a method in which the antibody variable region sequences are expressed on the surface of yeast cells, one antibody per cell.

17. Another technique developed in the 1990s and described in the patent involves generating transgenic mice by replacing that part of the mouse genome carrying the antibody genes with the human counterpart. When interrogated with the target protein of interest, these transgenic mice make human rather than murine antibodies to the target protein.

The patent description – background to the invention

18. The patent relates to antigen binding proteins that bind to proprotein convertase subtilisin kexin type 9 (´PCSK9´) and methods of using and making the antigen binding proteins.

19. As regards the background to the invention, the patent initially states that PCSK9 is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein (para. [0002]). LDLR is a protein receptor expressed on the surface of liver cells that is important for removing Low density lipoprotein cholesterol (LDL-C), which is transported by Low density lipoprotein (LDL) throughout the body. Typically, LDLRs on the cell surface bind to LDL-C, transport LDL-C into the cell where it is broken down for use by the body, and are then recycled to the cell where they can continue transporting LDL-C from the bloodstream into the cell.

20. Still according to the background section of the patent, in vitro experiments had shown that adding PCSK9 to HepG2 cells lowers the levels of cell surface LDLR. Experiments with mice had shown that increasing PCSK9 protein levels decreases levels of LDLR protein in the liver, while PCSK9k knockout mice have increased levels of LDLR in the liver. Additionally, various human PCSK9 mutations that result in either increased or decreased levels of plasma LDL had been identified. PCSK9 had been shown to directly interact with the LDLR protein, be endocytosed along with the LDLR, and to co-immunofluoresce with the LDLR throughout the endosomal pathway.

21. Moreover, according to the background section of the patent, it had been found that PCSK9 binds to the EGFa domain within the LDLR, referencing Zhang et al., 2007 (submitted as C4 in these proceedings). As the patent further states, degradation of the LDLR by PCSK9 had not been observed and the mechanism through which it lowers extracellular LDLR protein levels is uncertain. Selective inhibition of the PCSK9 gene in hyperlipidemic mice using an antisense oligonucleotide (ASO) resulted in significant reductions in hepatic PCSK9 mRNA levels, with concomitant reductions in total cholesterol and LDL (para. [0002]).

22. The patent explains as further background that PCSK9 is a prohormone-proprotein convertase in the subtilisin (S8) family of serine proteases (para. [0003]). Prohormone-proprotein convertases are expressed as zymogens and they mature through a multistep process. Humans have nine prohormone-proprotein convertases. Crystal and NMR structures of different domains from mouse furin and PC1 revealed subtilisin-like pro- and catalytic domains, and a P domain directly C-terminal to the catalytic domain. Based on the amino acid sequence similarity within this subfamily, all seven members were predicted to have similar structures.

23. The function of the pro-domain in the multistep process is twofold. The pro-domain first acts as a chaperone and is required for proper folding of the catalytic domain. Once the catalytic domain is folded, autocatalysis occurs between the pro-domain and catalytic domain. Following this initial cleavage reaction, the pro-domain remains bound to the catalytic domain where it then acts as an inhibitor of catalytic activity. When conditions are correct, maturation proceeds with a second autocatalytic event at a site within the pro-domain. After this second cleavage event occurs, the pro-domain and catalytic domain dissociate, giving rise to an active protease (para. [0004]).

24. Finally, the background section of the patent explains that autocatalysis of the PCSK9 zymogen occurs between Gln152 and Ser153 (VFAQ|SIP), and had been shown to be required for its secretion from cells. A second autocatalytic event at a site within PCSK9's pro-domain had not been observed. Purified PCSK9 is made up of two species that can be separated by nonreducing SDSPAGE; the pro-domain at 17 Kd, and the catalytic plus C-terminal domains at 65 Kd. PCSK9 has not been isolated without its inhibitory pro-domain, and measurements of PCSK9's catalytic activity have been variable (para. [0005] of the patent description).

Procedural background and the impugned order

25. On 1 June 2023, Sanofi brought a revocation action against the patent in the Central Division, section Munich (CDM). Also on 1 June 2023, Amgen brought an infringement action related to the patent to the Local Division Munich against Sanofi and Regeneron. Regeneron filed a counterclaim for revocation, which was subsequently, with the agreement of the parties, referred to the CDM, where it was combined with the pending revocation action lodged by Sanofi. The infringement action was stayed.

26. The CDM found that the patent lacks inventive step. The CDM revoked the patent in its entirety with effect for all of the Territories and ordered that Amgen bear Respondents' legal costs to an amount of 1.375 million Euro.

27. Amgen timely filed the appeals.

28. The oral hearing before the Opposition Division took place from 31 March to 3 April 2025 and at the end thereof the Opposition Division orally announced that it rejected the opposition. Thereafter, the oral hearing in the present appeal proceedings, originally scheduled for 22 May 2025, was postponed to 12 August 2025, in order to allow the parties to comment on the decision (with grounds) of the Opposition Division, issued on 21 May 2025.

SUMMARY OF THE PARTIES' SUBMISSIONS AND REQUESTS

29. In the Statements of grounds of appeal Amgen argues that the CDM was wrong to find a lack of inventive step. Amgen submits that the CFI committed errors in the legal approach to the inventive step assessment, more in particular applied the wrong legal framework for whether the skilled person had a reasonable expectation of success that the envisaged solution would solve the problem underlying the invention. Amgen also complains that the CDM proceeded from a fundamentally wrong interpretation of the prior art. Amgen still disputes the further grounds for revocation brought forward by Respondents and in that regard refers to its arguments raised before the CDM, including its conditional reliance on the

auxiliary requests brought forward at first instance should the Court of Appeal consider the patent as granted to be invalid.

30. Amgen requests that the impugned decisions be set aside, that the patent be maintained as granted in all of the Territories, and that Respondents be ordered to pay Amgen's legal costs in an amount of 1.375 million Euro in each of the first instance proceedings and to bear Amgen's legal costs in both appeal proceedings.

31. Respondents support the impugned decisions. They request that the appeal be rejected, that the decisions, including the cost decisions, be upheld either on the ground of lack of inventive step or any other ground, that the auxiliary requests be dismissed, and that Amgen be ordered to bear the Respondents' legal costs with respect to the appeal proceedings.

32. In case the Court of Appeal would allow the appeal, Respondents maintain their further arguments for revocation brought forward before the CDM, notably that the patent has been amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 138(1) sub c in connection with Article 123(2) of the European Patent Convention ("EPC")), the invention is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 138(1) sub b in connection with Article 83 EPC) and/or does not involve an inventive step for further reasons (Article 138(1) sub a in connection with Article 56 EPC). Respondents no longer argue that the claimed subject matter of the patent cannot claim priority from P3 and that it is not new, which arguments were advanced at first instance but rejected by the CDM.

GROUNDS FOR THE DECISION

Procedural objection

33. Respondents have objected to par. 72 to 82 of Amgen's Statement of grounds of appeal, as being new on appeal. The Court of Appeal sees no reason to use its discretion to disregard these arguments. The relevant paragraphs concern comments to an expert declaration by Respondents' expert Prof. Horton in the last written pleadings before the oral hearing, to which Amgen has not been able to respond in writing. With the relevant paragraphs Amgen also and more in particular substantiates its objection to various considerations in the impugned order, more in particular CFI's rejection of Amgen's argument that the skilled person did not have a reasonable expectation of success. Naturally, that was not possible during the proceedings at first instance. These statements and the only new exhibit that Amgen has submitted in this context (the effectiveness of statins available on the market) are furthermore not of such a nature that it would be burdensome for Respondents to comment on, which it has indeed extensively done in the Statement of response.

The relevant date of the patent

34. Respondents argued at first instance that the earliest priority date that the patent could validly rely on was 4 August 2008 (the filing date of P4). The CDM found that the patent can successfully claim priority from P3. Amgen has not appealed against this and Respondents have not maintained on appeal their arguments at first instance that the patent is not entitled to priority from P3. The priority date of the patent is therefore 9 January 2008. The OD came to the same conclusion in its decision of 21 May 2025.

Skilled person

35. The CDM held that the skilled person is a team including someone having a university degree in biological sciences (or biochemistry) and several years of (post-doctorate) experience in the field of antibody technology. The team also includes a researcher with a number of years post-doctorate research

experience who is undertaking preclinical research into the treatment of cardiovascular diseases, and who has an interest in PCSK9 biology with respect to the role and function of PCSK9 in regulating LDL levels.

36. Amgen complains that the CDM included someone with experience in the field of antibody technology and left out someone who has experience in drug discovery. It argues that by including someone with knowledge of and experience in antibody technology, the CDM has wrongly included knowledge of the invention and thus leads to hindsight. Further, by leaving out someone who has experience in drug discovery, the CDM has taken away the realistic perspective that the skilled person would have on the prior art, so Amgen argues.

37. Taking into account the object of the invention, as set out below, the Court of Appeal agrees that the skilled person is more appropriately defined more generally as a team of scientists having experience in drug discovery and development as it is conducted in the pharmaceutical industry. At the priority date this would include someone having experience in the field of antibody technology, as Respondents rightly noted, but would also include scientists having experience in other areas of drug development, such as small molecules.

The object of the invention

38. In view of the claims as interpreted in light of the patent description, the underlying problem that the invention purports to solve is to provide a therapeutically effective treatment or prevention of hypercholesterolemia or atherosclerotic disease or other conditions related to elevated serum cholesterol levels. The provision of an antibody or the use of PCSK9 as a target to regulate LDLR levels should not be included in the problem that the invention purports to solve, as this already points to the solution provided by the invention and would introduce an element of hindsight in the inventive step assessment.

Claim interpretation

39. The principles applicable to claim construction have been set out by this Court in its final order in UPC_CoA_335/2023 (Order of 26 February 2024, as rectified, *NanoString v 10x Genomics*). The patent claim is not only the starting point but the decisive basis for determining the protective scope of a European patent under Art. 69 EPC in conjunction with the Protocol on the Interpretation of Art. 69 EPC. The interpretation of a patent claim does not depend solely on the strict, literal meaning of the wording used. Rather the description and the drawings must always be used as explanatory aids for the interpretation of the patent claim and not only to resolve any ambiguities in the patent claim. The patent claim is to be interpreted from the point of view of a person skilled in the art. In applying these principles, the aim is to combine adequate protection for the patent proprietor with sufficient legal certainty for third parties.

Claim features

40. The Court of Appeal uses the same feature breakdown of Claim 1 as the CDM, which the parties have also used in their pleadings. The division into claim features is for reference only. It is reminded that claim features must always be interpreted in the light of the claim as a whole.

F1. A monoclonal antibody or an antigen-binding fragment thereof
F2. for use
F2.1 in treating or preventing hypercholesterolemia or an atherosclerotic disease related to elevated serum cholesterol levels;
or

F2.2 in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels.

F3. The monoclonal antibody or the antigen-binding fragment thereof binds to the catalytic domain of a PCSK9 protein of the amino acid sequence of SEQ ID NO: 1.

F4. The monoclonal antibody or the antigen-binding fragment thereof prevents or reduces the binding of PCSK9 to LDLR.

41. The parties debated about the interpretation of some of these features, which therefore requires discussion.

42. Amgen agrees that, since the claims are drafted in 'medical use-format', it is an inherent claim feature that the claimed product must be objectively suitable for the claimed use, i.e. be therapeutically effective.

43. The CDM held that the skilled person would understand from the description that the claimed treatment is not limited to a particular lowering of cholesterol levels as long as there is some (measurable) reduction of cholesterol levels in vivo and provided the therapy is safe. It also noted with reference to claims 6 and 7 of the patent, that the fact that the claimed use encompasses the administration of the claimed antibodies together with at least one other cholesterol-lowering agent, notably statins, confirms the understanding of the skilled person that also a (very) small cholesterol-lowering effect caused by the claimed antibodies can be "therapeutically effective" in the sense of the claimed treatments.

44. Amgen disputes that the claims are not limited to any particular degree of reduction of the binding of PCSK9 to LDLR and submits that 'when assessing the motivation of the skilled person at the priority date to solve the problem underlying the invention, the goal of the skilled person must be seen to provide a meaningful treatment of the relevant diseases that results in a therapeutic benefit compared to treatments known in the prior art'.

45. The Court of Appeal first notes that the question of whether conclusions can be drawn from the subject matter of a dependent claim and its features when interpreting the main claim, depends on the circumstances of the individual case. If the dependent claim is only adding an additional feature that does not provide a more specific description of the features of the main claim, it generally argues against the possibility of drawing conclusions about the interpretation of the main claim from this dependent claim.

46. Where the interpretation of claim 1 of the patent is concerned, this must be established on the basis of its own claim features only. There is no ground for interpreting claim 1 in the light of the additional feature in claims 6 and 7 prescribing administration of the claimed antibodies together with at least one other cholesterol-lowering agent, notably statins, as the CDM has done. This additional feature may lead to a different interpretation of the level of required therapeutic effect of the claimed antibodies where it concerns claims 6 and 7, but cannot be considered when interpreting claim 1, which covers the treatment with the claimed antibodies as the only administered medicament, which therefore must be therapeutically effective on its own.

47. The Court of Appeal further agrees with Amgen that the implicit requirement that the claimed antibodies must be effective as a medicament for the treatment or prevention of the diseases mentioned in the claim means that not *any* lowering of cholesterol levels, let alone any binding of PCSK9 to LDLR as Respondents argue, suffices. Any lowering or binding may bring about an effect, but that is not necessarily enough to bring about a *therapeutic* effect. This requires that the claimed treatment causes a noticeable improvement of the medical condition of the patient suffering from the disease mentioned in the claim. In that sense, Amgen is right that the treatment must be meaningful.

48. The fact that the skilled person does not derive any minimum required effect from the claim or the description, as the CDM rightly noted, does not lead to another conclusion, since the feature of therapeutic effect does not follow from the claim language that is to be interpreted, but from the use of the medical use claim format.

49. That being said, the claims do not require any particular threshold regarding the *level* of therapeutic effect that the claimed product must achieve, as long as it is therapeutically effective in a meaningful way.

50. With respect to feature F3, especially the wording "binds to the catalytic domain of a PCSK9 protein", the CDM held that the catalytic domain is understood by the skilled person as the region consisting of amino acid residues 123 to 419 of human PCSK9 (SEQ ID NO: 1) and that the antibody must bind to at least one amino acid residue that lies within the catalytic domain. The CDM further held that the skilled person will understand that this feature is fulfilled when binding *also* takes place in the catalytic domain and prevents or reduces the binding of PCSK9 to LDLR. This means that it is not required that the antibody binds *solely* to amino acid residues within the catalytic domain. Neither is it required that antibodies bind to those amino acid residues within the catalytic domain that are directly involved in the interaction between PCSK9 and the EGFa domain of the LDLR. Only binding *exclusively* to the pro-domain or the V-domain is excluded.

51. Amgen does not dispute this interpretation as such but disputes the CDM's consideration that there is no apparent causal technical connection between the feature "binds to the catalytic domain" and the reduction of the binding of PCSK9 to LDLR and that therefore this feature cannot contribute to inventive step. This argument does not seem to concern claim interpretation as such, but rather the relevance of the technical effect of this feature when assessing whether the invention required inventive step, or was obvious as alleged by Respondents.

Added matter

52. Respondents argue that claims 1, 3, 5, 6, 7 and 8 add matter to the application as filed and earlier application as published, because the application is used as a reservoir to make arbitrary selections and artificially create new combinations in the granted claims.

Principles

53. Under Article 138(1)(c) EPC a European patent may be revoked if its subject-matter extends beyond the content of the application as filed or, if it was granted on a divisional application, extends beyond the content of the earlier application as filed.

54. In order to ascertain whether there is added matter contrary to Art. 123(2) EPC, the Court must thus first ascertain what the skilled person would derive directly and unambiguously using his common general knowledge and seen objectively and relative to the date of filing, from the whole of the application as filed, whereby implicitly disclosed subject-matter, i.e. matter that is a clear and unambiguous consequence of what is explicitly mentioned, shall also be considered as part of its content (UPC_CoA_382/2024, order of 14 February 2025, *Abbott v Sibio*, para. 52).

55. The underlying rationale for this requirement is that the patentee cannot claim more than he actually contributed to the state of the art at the priority date. Therefore, an amendment that is made after the priority date should not provide the skilled person with additional technically relevant information which was not derivable from the original application.

The disclosure of the application as filed

56. Like Respondents (par. 5.5.8. Revocation Statement), the Court of Appeal shall use the published text of WO2009/026558, (the parent application, submitted as Exhibit A1) as the 'application as filed'. The divisional application filed on November 7, 2019 has not been submitted as an exhibit separately but, as can be learned from the OD Decision, is identical to the parent application, with the original PCT claims included as 'Items'.

57. Respondents have at the oral hearing objected to reliance on item 1 and par. [0355], of the application as filed (hereinafter also simply "the application"), because these cannot be found in priority document P3. If Amgen wanted to rely thereon, it would mean that the priority date of P4 (4 August 2008) would apply with the consequence that earlier patent applications C2 and C3 would become prior art and novelty destroying, so Respondents argued.

58. This argument cannot be accepted. At first instance Respondents' priority argument solely relied on their allegation that the "catalytic domain" of claim 1 was only disclosed for the first time in P4 because P1-P3 used a different definition of "catalytic domain". No argument was made that the patent could not rely on the priority of P3 for lack of disclosure therein of the subject matter covered by Claim 1 / Item 1 and par. [0355] of the parent application and the identical application as filed. The CDM rejected Respondents' lack of priority arguments and held that the patent can successfully claim priority from P3.

59. As mentioned above, the validity of the priority claimed on the basis of P3 is not within the scope of the appeal. Respondent's argument would reintroduce a discussion on whether the claims have sufficient basis in P3 through the back door of an added matter argument and cannot be allowed. That is especially so since this was only raised at the oral hearing. There is thus no reason to disregard (the subject matter of) item 1 and any other paragraph in the application when assessing added matter.

60. There is also no reason why par. [0355] should be disregarded because Amgen has referred to it 'only' in its rejoinder. It did so in response to a further developed added matter argument by Respondents. Respondents had sufficient opportunity to respond thereto in their Statement of response on appeal but failed to do so.

61. It is also irrelevant whether and when Amgen referred to any particular paragraph in the application. The assessment of whether there is added matter is a question of law to be decided on the basis of the facts brought forward by the parties. The facts are the relevant claims and the application as filed. Since the test is whether the relevant claims have basis in the application *as a whole*, the Court is allowed to look at the entire document.

Claim 1

62. Respondents' main objection to claim 1 is that the *combination* of features cannot be found in the application. Allegedly, claim 1 represents a new combination of features generated by five arbitrary selections from various lists in the original application, the selections being:
    a. monoclonal antibody or an antigen-binding fragment thereof;
    b. the antibody binds to the catalytic domain of PCSK9
    c. the PCSK9 protein has the amino acid sequence of SEQ ID NO:1;
    d. the antibody blocks the PCSK9-LDLR interaction;
    e. the particular list of therapeutic indications.

a. monoclonal antibody

63. In par. [0013] several types of an antibody or an antigen-binding fragment thereof (hereinafter in short: antibody) are mentioned, but the skilled person would see that in lines 16-17: "*In some embodiments, the isolated antigen binding protein is a monoclonal antibody*" the monoclonal antibody is singled out compared to the more general language below: "*In some embodiments, the isolated antigen binding*

protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof' further down (lines 22-25).

64. Under the heading of 'Detailed description of certain exemplary embodiments' it is stated in par. [0160] that "*Antigen binding proteins (such as antibodies and functional binding fragments thereof) that bind to PCSK9 are disclosed herein*". The only specifically mentioned antigen binding protein is the human monoclonal antibody.

65. Par. [0201], [0216] and [0252] mention monoclonal, but not polyclonal, antibodies. Par. [0274] states that "*As described herein, an antigen binding protein that binds to PCSK9 can comprise a human (i.e., fully human) antibody and/or part thereof*." and mentions that "*According to certain embodiments, a hybridoma cell line expressing such a monoclonal antibody is provided*" and "*In certain embodiments, a purified human monoclonal antibody to human PCSK9 is provided*".

66. Under the heading of 'Preparation of Fully Human ABPs (e.g., Antibodies) par. [0300] and [0302] discuss the generation of human monoclonal antibodies. Par. [0306] mentions that through the use of XenoMouse® technology "*fully human monoclonal antibodies to a variety of antigens have been produced*".

67. In Example 1 it is stated that antibodies were raised in XenoMouse® mice, from which the skilled person would understand that monoclonal antibodies were obtained, as Amgen submitted with reference to par. [0307] and the patents referred to therein, and not sufficiently disputed by Respondents. Examples 13-17 use antibody 31H4, and also in Example 26 a fully human monoclonal antibody directed against PCSK9 is used. These examples report lowering total serum cholesterol using these monoclonal antibodies.

68. When reading the application as a whole, and the clear emphasis therein on monoclonal antibodies, the skilled person would without doubt understand that the monoclonal antibody is the preferred one.

b. the antibody binds to the catalytic domain of PCSK9

69. Paragraph [0037] when describing that the invention comprises a neutralizing antibody that binds to PCSK9 and reduces a low density lipoprotein receptor (LDLR) lowering effect of PCSK9 on LDLR, specifically states that "*In some embodiments, the antibody binds to the catalytic domain of PCSK9*". It does not mention other domains.

70. In par. [0248] binding to the catalytic domain of PCSK9 is mentioned as the only binding site in the first sentence. Binding to the catalytic domain is also central in par. [0264]. In par. [0334] in the first paragraph under the heading 'Exemplary epitopes' only an epitope on the catalytic domain is specifically mentioned.

71. In par. [0274] under the heading 'Human Antigen Binding Proteins (e.g. Antibodies) the antibodies 21B12, 16F12 and 31H4 are singled out. This is also true for par. [0317].

72. Antibodies 21B12, 16F12 and 31H4 bind to the catalytic domain. For 31H4 this is mentioned in Example 29, par. [0508]: "*31H4 binds to PCSK9 in the region of the catalytic site and makes contacts with amino acid residues from both the prodomain and catalytic domain*"; for 21B12 this is clear from Example 30: "*21B12 binds to the catalytic domain of PCSK9, has a distinct binding site from 31H4 and can bind to PCSK9 simultaneously with 31H4*" and "*21B12 interacts with amino acid residues from PCSK9's catalytic domain*". In Examples 10 and 30 it is mentioned that "*16F12 and 31H4 appear to share a similar epitope*".

73. The examples are mainly carried out with antibodies 31H4, 21B12 and 16F12 that bind to the catalytic domain. Example 28 has the heading "*The LDLR EGFa domain binds to the catalytic domain of PCSK9*", Example 29 has the heading "*31H4 interacts with amino acid residues from both the pro- and catalytic domains of PCSK9*" and Example 30 "*21B12 binds to the catalytic domain of PCSK9, has a distinct binding site from 31H4 and can bind to PCSK9 simultaneously with 31H4*".

74. From these paragraphs, the skilled person understands the focus and preference to be on antibodies binding to the catalytic domain. The mere fact that embodiments binding to other domains are mentioned in the application does not alter this. Neither does the fact that Examples 13-17, 26 and 29 are carried out with antibody 31H4 which binds to both the pro- and catalytic domain lead to a different conclusion. As considered under claim construction, the antibodies must at least *also* bind to the catalytic domain (which antibody 31H4 does), only *exclusive* binding to the V-domain or Pro-domain being excluded.

c. the PCSK9 protein has the amino acid sequence of SEQ ID NO:1

75. In par. [0037] the statement that in some embodiments, the antibody binds to the catalytic domain of PCSK9, is immediately followed by "*In some embodiments, the antibody binds to an epitope within residues 31-447 of SEQ ID NO:3*", thus providing a link between binding to the catalytic domain and residues 31-447 of SEQ ID NO:3. In par. [0040] it is again noted that: "*The antibody binds to PCSK9 at a location within residues 31-447 of SEQ ID NO:3*". Binding to a PCSK9 protein having the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:1 is further mentioned in various paragraphs of the application.

76. The skilled person appreciates that residues 31-447 of SEQ ID NO:3 is the same as SEQ ID NO:1. Par. [0355] teaches the skilled person that in the description references to specific amino acid positions were with reference to SEQ ID NO:1 and also that SEQ ID NO:3 – other than SEQ ID NO:1 – includes additional 30 amino acids representing the signal sequence. An amino acid position in SEQ ID NO:1 will therefore correspond to an amino acid position 30 amino acids further into the protein in SEQ ID NO:3. Amgen has undisputedly submitted that the skilled person knows that the signal sequence is cleaved off on the secretory pathway, so that in physiological context SEQ ID NO: 1 and 3 are the same.

77. Par. [0037] thus discloses that the antibody binds to an epitope in SEQ ID NO:1 within the catalytic domain of PCSK9. Binding to an epitope within the catalytic domain of a PCSK9 protein is described in Examples 28-31.

d. the antibody blocks the PCSK9-LDLR interaction

78. The skilled person would undoubtedly understand from the application as a whole that the invention is about an antibody blocking PCSK9:LDLR binding.

79. In the background section (par. [0003]) the role of PCSK9 in regulating LDLR levels is discussed, mentioning that increased PCSK9 levels decrease levels of cell surface LDLR.

80. Par. [0013] identifies PCSK9 as the targeted antigen with the aim of lowering LDL / increasing LDLR: "*In some embodiments, the isolated antigen binding protein reduces binding of PCSK9 to LDLR. In some embodiments, the isolated antigen binding protein decreases an amount of LDL present in a subject when administered to the subject. In some embodiments, the isolated antigen binding protein decreases an amount of serum cholesterol present in a subject when administered to the subject. In some embodiments, the isolated antigen binding protein increases an amount of LDLR present in a subject when administered to the subject*."

81. Inhibiting binding of PCSDK9 to LDLR is explicitly mentioned as an aspect of the invention (par. [0019]) also in relation to treating or preventing a condition associated with elevated serum cholesterol levels in

a patient (e.g. par. [0018] and [0021]). In numerous paragraphs the method of increasing LDLR protein levels by administering an isolated antigen binding protein is mentioned.

82. From par. [0160] the skilled person understands that the function of the antigen binding proteins is to bind to PCSK9 to block or reduce its ability to interact with other substances, whereby LDLR is the only example of such a substance. Par. [0161] explains that altering the interactions between PCSK9 and LDLR can increase the amount of LDLR available for binding to LDL, which in turn decreases the amount of serum LDL in a subject, resulting in a reduction in the subject's serum cholesterol level.

83. The second to last sentence of par. [0161] referred to by Respondents does not alter that conclusion. Even though there may be antigen binding proteins that allow the binding between PCSK9 and LDLR (but still preventing or reducing the adverse activity of PCSK9 on LDLR), it is clear from par. [0229] that an antigen binding protein with this mechanism (such as 31A4) is considered a weak neutraliser, while the antigen binding proteins of Table 2, which bind to PCSK9 and thereby prevent or reduce PCSK9:LDLR binding, of which 31H4 and 21B12 are examples, are strong neutralisers. It is clear throughout the application that these are the preferred antibodies.

84. Par. [0248] connects binding to the catalytic domain to blocking the PCSK9-LDLR interaction: ”*In some embodiments, the ABP binds to the catalytic domain in a manner such that PCSK9 cannot bind or bind as efficiently to LDLR*”.

e. list of therapeutic indications

85. Hypercholesterolemia (defined in par. [0167] as a condition in which cholesterol levels are elevated above a desired level) is mentioned in par. [0029] and in par. [0166] in direct connection with the ability of PCSK9 to decrease the amount of LDLR that is available to bind to LDL, and therewith the ability to increase the amount of LDL in a subject.

86. Par. [0250] describes that the PCSK9 antigen binding proteins are useful for treating cholesterol related disorders (or "serum cholesterol related disorders") such as hypercholesterolemia.

87. Under the heading of ’Certain Therapeutic Uses and Pharmaceutical Compositions’ par. [0358] discusses that PCSK9 activity correlates with a number of human disease states such as hypercholesterolemia and that modulating PCSK9 activity can be therapeutically useful. It goes on to state that an antigen binding protein to PCSK9 is used to modulate at least one PCSK9 activity (e.g., binding to LDLR) and that such methods can treat and/or prevent and/or reduce the risk of disorders that relate to elevated serum cholesterol levels or in which elevated cholesterol levels are relevant.

88. Par. [0359] then states that disorders that relate to, involve, or can be influenced by varied cholesterol, LDL, or LDLR levels can be addressed by various embodiments of the antigen binding proteins. Among the cholesterol related disorders mentioned where the antigen binding proteins can be helpful in prevention or treatment are atherosclerotic diseases, while the use of antigen binding proteins to reduce the risk of recurrent cardiovascular events is also mentioned.

89. Given these disclosures in the application the skilled person understands from the application as a whole that the antibody of the invention is primarily aimed at binding to PSCK9 in order to prevent PCSK9:LDLR binding, resulting in raised LDLR levels, leading to lower LDL levels, for the therapeutic use of treating or preventing diseases associated with elevated serum cholesterol levels. Par. [0359] clearly qualifies hypercholesterolemia, atherosclerotic disease and recurrent cardiovascular event to be such diseases. The addition of the words ’related to elevated serum cholesterol levels’ to these diseases in the claim language does not provide the skilled person with information that was not derivable from the application.

The combination of features of claim 1

90. Literal support is not required to comply with Art. 138(1)(c) EPC. Neither is it required that all features of the claim can be found in one paragraph or one example of the application, as Respondents seem to suggest. It is sufficient if the skilled person can derive the subject matter of the claim from the application as a whole. The argument that each of the features required a selection from lists and that there was no pointer for the skilled person to the specific combination of the features of claim 1 must be rejected. The fact that the application also provides alternatives for features of claim 1, does not mean the skilled person is required to make an arbitrary selection from various lists. As follows from the above, where the application provides for alternatives, it is clear to the skilled person which of the alternatives is preferred.

91. The features of claim 1 are also linked to each other in various paragraphs of the application. Par. [0037] links binding to an epitope in PSCK9 amino acid sequence SEQ ID NO:1 to the catalytic domain of PCSK9. Par. [0248] links binding to the catalytic domain to preventing PCSK9:LDLR binding. Par. [0274] links monoclonal antibodies to binding to PCSK9; while the same paragraph singles out antibodies 21B12, 16F12 and 31H4, which are monoclonal antibodies that bind to the catalytic domain. Examples 28-31 are carried out with these antibodies and show that these can be useful for inhibition of PCSK9:LDLR interaction. This is explained in par. [160-161] to result in a reduction in a patient's serum cholesterol level. Par. [0358] teaches that modulating PCSK9 activity can be therapeutically useful, among others for treating or prevention of diseases related to elevated cholesterol levels, such as hypercholesterolemia, atherosclerotic diseases and recurrent cardiovascular events. The connection between the use of 31H4 or 21B12 or 16F12 (which the skilled person understands to be monoclonal antibodies that bind to the catalytic domain) for the treatment of a patient exhibiting a cholesterol related disorder (in which a reduction in cholesterol (such as serum cholesterol) can be beneficial, is made in par. [0480], which reports that following treatment, it is found that patients undergoing treatment with the PCSK9 antibody have reduced serum cholesterol levels, in comparison to patients that are not treated. As such, there is also no 'intermediate generalisation' as Respondents unsuccessfully asserted. Thus, the preferred features taken together, as well as the various links between the features in the application, the combination of the claimed features was clearly and unambiguously derivable for the skilled person from the whole of the application as filed.

92. To conclude, considering the above disclosures of the application, read in context of the application as a whole, the skilled person can clearly and unambiguously derive that the preferred antibody disclosed therein is monoclonal, binds to the catalytic domain of PCSK9 having the amino acid sequence of SEQ ID NO:1, with the effect of blocking or reducing its ability to interact with LDLR, and with the aim of using such antibody in the treatment or prevention of diseases associated with elevated cholesterol levels, including those mentioned in the claim.

Claims 3 and 5

93. Claim 3 protects the antibody according to claim 1 "in treating or preventing an atherosclerotic disease related to elevated serum cholesterol levels" and Claim 5 relates to an antibody "for use in reducing the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels".

94. Respondents have not provided other arguments why this would contravene Art. 123(2) EPC than those raised and rejected in relation to claim 1. Reference is made to the considerations above.

Claims 6 and 7

95. Claim 6 protects the antibody of the previous claims "administered together with at least one other cholesterol-lowering agent". Claim 7 specifies that this cholesterol lowering agent is a statin, optionally one selected from a group of several mentioned statins.

96. Par. [0367] of the application provides that an antigen binding protein to PCSK9 may be administered alone, prior to the administration of at least one other therapeutic agent; concurrent with the administration of at least one other therapeutic agent and subsequent to the administration of at least one other therapeutic agent.

97. Respondents argue that 'concurrently' must be read as 'together with' and so read claim 6 is a choice out of a list of three options for which there is no pointer. This argument fails. The skilled person appreciates the possibilities of administration of an antibody to be 'prior to', 'concurrent with' (the term used in par. [0367] of the application is not 'concurrently' as Respondents misrepresent) and 'subsequent to' administration of another therapeutic agent, as an alternative to the antibody being administered alone. He will understand these options to refer to the order of administration of the antibody relative to that of the administration of the other therapeutic agent. This can be either first the antibody, then the other ('prior to'), or the antibody at the same time as the other agent ('concurrent with'), or first the other agent and thereafter the antibody (subsequent to'). The first and last option are also referred to in the application as 'sequentially', the second then being described as 'simultaneously'. The common denominator of all this terminology is that they all express that *both* an antibody *and* another therapeutic agent are administered, i.e. 'together'. The skilled person would thus interpret the use of the wording 'together with' in claim 6 as a catch all term for either of the given possibilities for the order of co-administration, as opposed to the antibodies being administered alone.

98. Par. [0026] already mentions that the invention comprises a pharmaceutical composition comprising the disclosed antigen binding protein and an agent that elevates the availability of LDLR protein levels, the only agent mentioned being a statin. Similar wording is found in various other paragraphs. Administration of a therapeutically effective amount of PCSK9 antibody with a statin, e.g., simvastatin is mentioned in Examples 21 and 24. Example 24 teaches the skilled person "*that ABPs to PCSK9 produced further increases in LDLR availability when used in the presence of statins, demonstrating that further benefits can be achieved by the combined use of the two*".

99. Given the teaching of these paragraphs in the application, specifying that the cholesterol lowering agent of claim 6 is a statin does not provide new information to the skilled person.

Claim 8

100. Claim 8 adds to any of the preceding claims that the antibody is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a Fab fragment, an $F(ab)_2$ fragment, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody and an IgG4 antibody or an antigen-binding fragment thereof.

101. Respondents acknowledge that par. [0013] discusses these features as optional features of an antigen binding protein, but disputes an unambiguous basis for these to be options for a monoclonal antibody. As said, there is no need for all features to be found in one and the same paragraph. Based on the teaching of the application as a whole the skilled person understands the preferred antibody to be a monoclonal antibody and failing any indication to the contrary, he therefore understands these options to apply to monoclonal antibodies as well. As such, claim 8 does not extend the subject matter beyond the content of the application, as understood by the skilled person at the priority date.

Conclusion on added matter

102. The conclusion is that none of the added matter arguments raised by Respondents is successful. The OD came to the same conclusion on substantially similar grounds.

Sufficiency

103. Respondents have further argued that the patent must be revoked pursuant to Art. 138(1)(b) EPC because it does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

104. The rationale behind this requirement is that the grant of a patent monopoly cannot be justified if the claimed subject matter cannot be achieved by the skilled person on the basis of the patent description.

Principles

105. Sufficiency has to be examined on the basis of the patent as a whole, thus on the basis of the claims, description and drawings, from the perspective of the skilled person with his common general knowledge at the filing or priority date.

106. The test to be applied is whether the skilled person is able to reproduce the claimed subject matter on the basis of the patent without any inventive effort and without undue burden. An invention is sufficiently disclosed if the patent specification shows the skilled person at least one way – and in case of functional features: one technical concept – of performing the claimed invention.

107. Where a claim contains one or more functional features, it is not required that the disclosure includes specific instructions as to how each and every conceivable embodiment within the functional definition(s) should be obtained. A fair protection requires that variants of specifically disclosed embodiments that are equally suitable to achieve the same effect, which could not have been envisaged without the invention, should also be protected by the claim. Consequently, any non-availability of some embodiments of a functionally defined claim is immaterial to sufficiency, as long as the skilled person through the disclosure is able to obtain suitable embodiments within the scope of the claim.

108. The burden of presentation and proof lies with Respondents as the party invoking invalidity of the patent.

Assessment

109. In relation to inventive step, Respondents have argued that the skilled person would have arrived at antibodies within the scope of the claims. It asserted that at the priority date routine techniques existed both for producing and for screening monoclonal antibodies. With reference to Zhang (C4) Respondents have submitted that using the assay disclosed therein, the skilled person would have identified antibodies that bind to the catalytic domain and prevent or reduce the binding of PCSK9 to LDLR. This must then also apply when assessing sufficiency, especially since in this assessment the skilled person has the benefit of knowing the invention and the description.

110. Respondents admit this but nevertheless raise several issues that would prevent the skilled person from obtaining the claimed antibodies substantially across the claimed range without undue burden.

111. Respondents' argument that the skilled person would be unable to obtain antibodies that bind to the catalytic domain because this domain cannot be expressed and secreted in isolation must be rejected. The skilled person would find sufficient guidance to use the entire PCSK9 protein to raise antibodies that bind the catalytic domain. A further screening step would enable the skilled person to identify whether the antibodies obtained bind to at least one amino acid of the catalytic domain.

112. Respondents also unsuccessfully argue that X-ray crystallography is the only technique which can determine accurately if an antibody binds to the catalytic domain but is an undue burden because it is onerous, time consuming, unpredictable and may fail, and that other techniques do not reliably identify binding to the catalytic domain.

113. The patent discloses several methods to identify whether an antibody binds to the catalytic domain and shows that and how they can be used to identify antibodies that bind to the catalytic domain. These techniques include X-ray crystallography (Examples 29, 30, 34 - 36), domain binding assay (Examples 27, 40), scanning mutagenesis (Examples 18 and 39) and competition assay (Examples 10, 37, par. [0462], also referred to in Examples 29 and 30, last par.). Further methods were known at the priority date, such as hydrogen deuterium exchange and HDX-MS, which was used to identify the two key binding epitopes of H1-Fab in the patent application filed by Novartis before the priority date.

114. The mere fact that X-ray crystallography is laborious, time-consuming and/or challenging, does not automatically mean that such method constitutes undue burden. That is especially so when this method is generally accepted as the standard by which the most accurate results are obtained, as Respondents submit. A reasonable amount of trial and error does not prevent the invention from being enabled. Respondents have not substantiated that it would not be possible, or at least not without undue burden, to obtain co-crystals of PCSK9 antibodies with PCSK9 and to map its interaction site, e.g. by trying to repeat the crystallization experiments disclosed in the patent, where necessary optimising the conditions from the examples to obtain further antibodies than those explicitly disclosed.

115. In addition, the patent does not prescribe a specific screening method. It discloses several screening methods and others were known to the skilled person based on his common general knowledge. Even if the other disclosed or known methods would not be as accurate as X-ray crystallography and occasionally lead to a false positive or a false negative or have other flaws, this does not mean that these methods were unsuitable. Occasional failure is part of scientific work, especially in this field of technology. Rather, as Amgen has submitted, supported by expert statements of Dr. Rees, it was routine to use a combination of different epitope mapping techniques to determine the binding location of an antibody with more certainty, as is indeed also suggested in par. [0376] of the patent.

116. Respondents have not supported their arguments by any evidence showing that the screening methods disclosed in the patent and/or those known to the skilled person based on his common general knowledge would be unsuitable to enable the skilled person to identify whether an antibody binds to the catalytic domain without undue burden.

117. Respondents furthermore argue that the patent does not teach the skilled person how to produce the full breadth of antibodies falling within the scope of the claims: e.g., antibodies that bind epitopes within the EGFa-binding site (so-called 'EGFa mimics'), without undue experimentation. This is rejected. What Respondents brought forward only shows that Amgen has not produced such antibody itself. The fact that it would be tricky to produce one binding to any of the 15 amino acids in that region, as one of the inventors stated, does not constitute evidence that EGFa mimics cannot be produced at all.

118. In addition, as said, it is not required that each and every conceivable embodiment within the functional definition(s) of the claim is enabled. Respondents' line of argument about EGFa mimics, the three antibodies in bin 2 of Example 37 disclosed as co-binning with antibodies 31H4 and 21B12, antibodies that interfere with PCSK9:LDLR binding sterically and antibodies that block the PCSK9:LDLR interaction by allosteric mechanisms, fail already for that reason. In addition, Respondents have not provided evidence for their allegation that the patent does not enable antibodies within the scope of the claim.

119. Respondents also more generally argue that the claim is not enabled because it covers antibodies that bind far from PCSK9's binding site with LDLR and far from the binding sites of the 21B12 and 31H4 antibodies. It is noted that the claim not only requires that the antibody binds to the catalytic domain – which requires binding to at least one amino acid within that domain, but not binding to a specific epitope or amino acid residue within the catalytic domain – *but also* that it prevents or reduces PCSK9 from binding to LDLR. Respondents have not shown that the patent does not enable an antibody that satisfies these requirements.

120. Respondents have furthermore not brought forward anything that would justify the conclusion that the skilled person would seriously doubt that antibodies that satisfy the features of the claim, i.e. bind to the catalytic domain and prevent or reduce PCSK9:LDLR interaction, are therapeutically effective for the diseases mentioned in the claim. The patent teaches that lowering of LDL is linked to a reduction or prevention of hypercholesterolemia, atherosclerotic diseases related to elevated serum cholesterol levels and a reduction of the risk of a recurrent cardiovascular event related to elevated serum cholesterol levels. Examples 13-17, 19-21, 23 and 26 of the patent demonstrate that the antibodies of claim 1 have the in vivo effect of lowering LDL cholesterol levels. The skilled person would therefore understand the antibodies of claim 1 to be suitable for use as medicament as stated in claim 1.

121. To conclude, the Respondents have not shown that the skilled person based on the teaching of the patent, taking common general knowledge into account, would be unable to obtain further antibodies with the claimed functional properties in a reliable manner with a reasonable amount of trial and error and without undue burden. Respondents' complaint that the level of proof required is too high can be dismissed, already for the reason that no proof of a failed attempt to obtain suitable antibodies within the scope of the claim has been submitted at all. The attack on the validity of the claim based on lack of sufficiency is therefore unsuccessful. The OD came to the same conclusion on substantially similar grounds.

Inventive step

122. The question of whether the invention required an inventive step is at the heart of the dispute between the parties. One of Amgen's complaints is that the CDM applied the wrong test. Before turning to the parties' substantive arguments, the Court of Appeal will set out the principles to be applied when assessing inventive step.

Principles

123. A European patent is only validly granted for an invention if – apart from other requirements – it involves an inventive step. An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art (Art. 56 EPC)

124. National courts of the various EPC countries have different approaches and use different guidelines when assessing whether an invention involves an inventive step. One of those approaches is the so-called 'problem-solution-approach' used by the European Patent Office (EPO) and the Technical Boards of Appeal (TBA) of the EPO. In some jurisdictions, such as France, Italy, The Netherlands and Sweden, this approach is applied as well, but not necessarily as the only possible approach. In other jurisdictions, such as Germany and the UK, other approaches – sometimes referred to as more 'holistic' – are used. Despite the differences in approach, all of these are just guidelines to assist in the establishment of inventive step as required by Art. 56 EPC, that, when properly applied, should and generally do lead to the same conclusion.

125. The burden and presentation of proof with regard to the facts from which the lack of validity of the patent is derived and other circumstances favourable to the invalidity or revocation lies with the claimant in a revocation action (Art. 54 and 65(1) UPCA, R. 44(e)-(g), 25.1(b)-(d) RoP). Even though proof of certain facts, if contested, may be required, the assessment of whether the legal consequence for which the facts and circumstances have been submitted is justified, is a question of law.

126. The approach taken by the Unified Patent Court when establishing inventive step, which can already be derived from the Order of the Court of Appeal in *Nanostring/10X Genomics* (*supra*), is as follows.

127. It first has to be established what the object of the invention is, i.e. the objective problem. This must be assessed from the perspective of the skilled person (m/f – hereinafter referred to as 'it'), with its common general knowledge, as at the application or priority date (also referred to as the relevant date) of the patent. This must be done by establishing what the invention adds to the state of the art, not by looking at the individual features of the claim, but by comparing the claim as a whole in context of the description and the drawings, thus also considering the inventive concept underlying the invention (the technical teaching), which must be based on the technical effect(s) that the skilled person on the basis of the application understands is (are) achieved with the claimed invention.

128. In order to avoid hindsight, the objective problem should not contain pointers to the claimed solution.

129. The claimed solution is obvious when at the relevant date the skilled person, starting from a realistic starting point in the state of the art in the relevant field of technology, wishing to solve the objective problem, *would* (and not only: *could*) have arrived at the claimed solution.

130. The relevant field of technology is the field relevant to the objective problem to be solved as well as any field in which the same or similar problem arises and of which the person skilled in the art of the specific field must be expected to be aware.

131. A starting point is realistic if the teaching thereof would have been of interest to a skilled person who, at the relevant date, wishes to solve the objective problem. This may for instance be the case if the relevant piece of prior art already discloses several features similar to those relevant to the invention as claimed and/or addresses the same or a similar underlying problem as that of the claimed invention. There can be more than one realistic starting point and the claimed invention must be inventive starting from each of them.

132. The skilled person has no inventive skills and no imagination and requires a pointer or motivation that, starting from a realistic starting point, directs it to implement a next step in the direction of the claimed invention. As a general rule, a claimed solution must be considered not inventive / obvious when the skilled person *would* take the next step prompted by the pointer or as a matter of routine, and arrive at the claimed invention.

133. A claimed solution is obvious if the skilled person would have taken the next step in expectation of finding an envisaged solution of his technical problem. This is generally the case when results of the next step were clearly predictable, or where there was a reasonable expectation of success.

134. The burden of proof that the results were clearly predictable or the skilled person would have reasonably expected success, i.e. that the solution he envisages by taking the next step would solve the objective problem, lies on the party asserting invalidity of the patent.

135. A reasonable expectation of success implies the ability of the skilled person to predict rationally, on the basis of scientific appraisal of the known facts before a research project was started, the successful conclusion of that project within acceptable time limits.

136. Whether there is a reasonable expectation of success depends on the circumstances of the case. The more unexplored a technical field of research, the more difficult it was to make predictions about its successful conclusion and the lower the expectation of success. Envisaged practical or technical difficulties as well as costs involved in testing whether the desired result will be obtained when taking a next step may also withhold the skilled person from taking that step. On the other hand, the stronger a pointer towards the claimed solution, the lower the threshold for a reasonable expectation of success.

137. When the patentee brings forward and sufficiently substantiates uncertainties and / or practical or technical difficulties, the burden of proof that these would not prevent a skilled person from having a reasonable expectation of success, falls on the party alleging obviousness.

138. The fact that other persons or teams were working contemporaneously on the same project does not necessarily imply that there was a reasonable expectation of success. It may also indicate that it was an interesting area to explore with a mere hope to succeed.

Inventive step assessment

139. The above principles applied to the claims of the patent lead to the conclusion that the claims are not obvious.

140. The scientific research in the field of the mechanism of action of PCSK9 had at the priority date not reached the stage where the skilled person could have reasonably predicted that an antibody that blocks the interaction between PCSK9 and LDLR would be therapeutically effective in treating or preventing the diseases referred to in claim 1 or of reducing the risk associated with such diseases. As such, the skilled person, on the basis of a scientific appraisal of the state of the art at the priority date, did not have a reasonable expectation of success that an antibody approach would have the desired therapeutic effect in vivo. This will be explained below.

Lagace is a realistic starting point

141. Amgen unsuccessfully disputes that Lagace (C3) was a realistic starting point for the skilled person in search of a solution to the objective problem underlying the invention. Amgen has advanced that Lagace reports on a study of fundamental biological research on the mode of action by which PCSK9 reduces levels of LDLR, which does not address what expectations, technical hurdles or uncertainties the skilled person would have in mind when considering possible therapeutic approaches. According to Amgen the skilled person would have started from Graham (D19) because that is the only publication from before the priority date that provides in vivo data of a therapeutic approach that targets PCSK9.

142. The Court of Appeal disagrees. Even if the skilled person who was looking for a solution to its problem was interested in Graham and the development of antisense oligonucleotides suggested therein, that does not prevent Lagace from being a realistic starting point as well. As said, there may be more than one realistic starting point, and an invention must involve inventive step starting from each of them.

143. The skilled person would at least *also* be interested in Lagace. The title of the publication is ”S*ecreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice*” and the abstract mentions that experiments have been carried out from which it is concluded ”*that secreted PCSK9 associates with the LDLR and reduces hepatic LDLR protein levels*”. It specifically mentions that ”*inhibitors of the protease [PCSK9] would be of therapeutic benefit for the treatment of hypercholesterolemia*”. It was thus directed to a similar purpose as that of the invention and would have been of interest to a skilled person who wanted to develop a treatment for hypercholesterolemia, atherosclerotic disease or other conditions related to elevated serum cholesterol levels (hereinafter also

referred to as hypercholesterolemia and similar diseases). The Court of Appeal further incorporates by reference the considerations of the CDM in par. 8.13 to 8.27 of the impugned decision and agrees with its conclusion based thereon that Lagace is a realistic starting point.

144. The mere fact that Lagace is not a paper about therapeutic approaches to target PCSK9 with the associated expectations and technical hurdles, as Amgen brought forward, does not alter that. In view of the objective problem that the skilled person seeks to solve, any possible target that plays a role in LDLR levels would be of interest to the skilled person. At the priority date PCSK9 was already identified as such a target. As Amgen itself states (SoGA par. 51), Lagace seeks to enhance the understanding of the mechanism by which PCSK9 reduces levels of LDLR. It is not disputed – and in fact at the heart of Amgen's appeal – that a proper understanding of PCSK9's mechanism of action is relevant for and logically precedes a detailed discussion on therapeutic approaches to target PCSK9.

The teaching of Lagace

145. The parties disagree on the conclusions a skilled person would draw from Lagace, in particular from the last paragraph "*If PCSK9 functions as a secreted factor as suggested by the current data, then additional approaches to neutralize its activity, including the development of antibodies to block its interaction with the LDLR or inhibitors to block its action in plasma, can be explored for the treatment of hypercholesterolemia*.". This last paragraph in Lagace will be understood by the skilled person in the context of the entire publication, which will be discussed below.

146. Lagace mentions in its Introduction paragraph several earlier studies involving PCSK9 and its role in LDLR levels. It describes that the biological activity of PCSK9 was revealed through overexpression studies in mice, which showed a reduction of the amount of LDLR in liver.

147. Lagace finds confirmation that PCSK9 functions normally to regulate LDLR protein levels in loss-of-function studies in humans and mice. With reference to Cohen 2005 (C16), Lagace describes that "*Individuals who are heterozygous for a nonsense mutation in allele PCSK9 have significantly lower plasma LDL cholesterol levels, suggesting that a reduction in PCSK9 activity leads to an increase in LDLRs*".

148. With reference to Rashid 2005 (C25) Lagace states that "*These conclusions were supported by studies in PCSK9-knockout mice, which revealed that loss of PCSK9 resulted in increased numbers of LDLRs in hepatocytes, accelerated plasma LDL clearance, and significantly lower plasma cholesterol levels*".

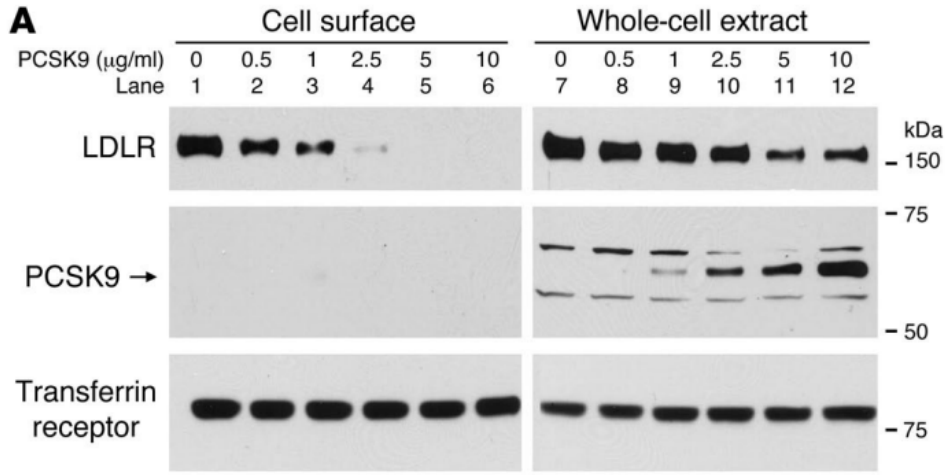
149. Furthermore, with reference to Cohen 2006 (C28) Lagace describes that "*In the most recent studies, humans heterozygous for loss-of-function mutations in PCSK9 were shown to have a significant reduction in the long-term risk of developing atherosclerotic heart disease*".

150. Lagace concludes that the genetic data from humans and the in vivo studies in mice demonstrate that one function of PCSK9 is to reduce the number of the LDLRs but also notes that the mechanism by which PCSK9 reduces the number of LDLRs is still undetermined: "*For example, it is unclear whether PCSK9 acts to destroy LDLRs in the secretory pathway or whether it acts outside of the cell*".

151. Lagace's contribution is that "*In the current studies, we provide evidence that extracellular PCSK9 can be internalized by cultured liver cells and fibroblasts in a manner that is largely dependent on LDLRs. Incubation with extracellular PCSK9 led to loss of LDLRs from the cell surface and accelerated destruction of LDLRs in liver-derived cells. Finally, we demonstrate that increased PCSK9 levels in the circulation of mice leads to diminished liver LDLR protein and increased plasma cholesterol levels.*"

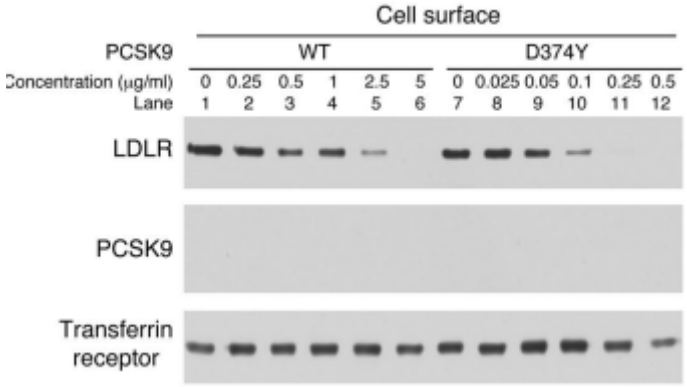
152. Lagace performs and describes several experiments, among which the quantification of the concentration and determination of the physiological range of PCSK9 concentration in human plasma. For this purpose, plasma levels of PCSK9 were quantified in 72 volunteers. The results showed that

plasma levels ranged from approximately˜50 to approximately˜600 ng/ml. Lagace concludes from this that these measurements demonstrate that considerable amounts of PCSK9 circulate in plasma and provided a range of physiologically relevant PCSK9 concentrations. Lagace then performed an experiment to determine whether the secreted form of PCSK9 can reduce the number of LDLRs. The results are shown in Figure 2A:



153. Lagace states: "As shown in Figure 2A, the number of cell-surface LDLRs declined by approximately 50% after incubation with the physiologically relevant concentration of 0.5 μg/ml PCSK9 (lane 2) and became nearly undetectable after exposure to 2.5 μg/ml PCSK9 (lane 4).

154. Figure 3 of Lagace (see below) according to the Legend shows "Increased cell association and LDLR degradation by addition of purified mutant PCSK9 (D374Y) to the medium of HepG2 cells". The experiment was carried out to determine whether a known PCSK9 mutant that causes hypercholesterolemia increases the activity of PCSK9 in a cell-based assay, by adding varying amounts of wild-type PCSK9 and the PCSK9 mutant D374Y and showed that the mutant was at least 10-fold more active. Lagace does, however, not provide a quantification for the results shown.



155. Under the heading 'Discussion" Lagace notes (inter alia) that "*In the current report, we demonstrate that endogenous PCSK9 is rapidly secreted from cells and that secreted PCSK9 destroys LDLRs when added to the medium of cultured HepG2 cells and mouse primary hepatocytes. The effective concentration of PCSK9 required to reduce the number of LDLRs in cultured cells was within the range of plasma concentrations measured in human plasma*" and "*Finally, we show that PCSK9 was present in plasma of transgenic mice and that the secreted protein was active in destroying hepatic LDLRs*."

156. In relation to the mode of action of PCSK9, Lagace mentions (inter alia) the following. "*Recent studies by Maxwell et al. (26) showed that overexpression of PCSK9 in HepG2 cells induced the degradation of LDLR intracellularly in a post-ER compartment*." and "*Considered together, the available data now suggest that PCSK9 can function both extracellularly and intracellularly, but we do not know which pathway predominates under normal and/or pathologic conditions. Currently, all studies suggesting that the protein functions intracellularly have been performed using PCSK9 overexpression [which] may permit association of PCSK9 and the LDLR in an intracellular compartment that does not occur physiologically. In the current studies, we were able to demonstrate that physiologically relevant concentrations of PCSK9 could significantly reduce the number of cell-surface LDLRs when added to HepG2 cells*".

157. Lagace then mentions that additional studies to determine the relative contribution of extracellular PCSK9 in the regulation of LDLR protein levels will require determining whether the infusion of PCSK9 into the circulation of PCSK9-knockout mice will decrease the number of LDLRs in liver and raise plasma cholesterol levels.

158. The final paragraph of Lagace then reads as follows: "*The genetic data from humans with loss-of-function mutations in PCSK9 combined with the studies in knockout mice that lack PCSK9 clearly indicate that inhibitors of the protease would be of therapeutic benefit for the treatment of hypercholesterolemia. Inasmuch as overexpression of the catalytically inactive form of PCSK9 in mice did not alter LDLR protein levels (9), an inhibitor of PCSK9's protease activity in the ER should be sufficient to block its ability to reduce LDLR protein levels. If PCSK9 functions as a secreted factor as suggested by the current data, then additional approaches to neutralize its activity, including the development of antibodies to block its interaction with the LDLR or inhibitors to block its action in plasma, can be explored for the treatment of hypercholesterolemia*."

159. Lagace thus clearly presents PCSK9 as a target of interest to the skilled person who wishes to develop a treatment for hypercholesterolemia and similar diseases. Lagace also teaches the skilled person that the experiments that were carried out show that an extracellular pathway of PCSK9 exists. In their joint statement prepared for Australian proceedings between the parties (hereinafter: the joint statement), Dr. Parker and Prof. Horton, party-experts on the side of Amgen and Respondents respectively, confirm the interest in PCSK9 as a target for the treatment of cholesterolemia and similar diseases: "*We agree that the human genetic validation was very strong, and it was clearly desirable to seek a PCSK9 inhibitor to reduce LDL levels. The genetic validation of a drug target is rare and in this case was the reason multiple pharmaceutical companies had PCSK9 inhibition programs*." (D95, par. 2.2)

160. The Court of Appeal agrees with the CDM that at the priority date the skilled person, starting from Lagace, had a strong incentive to block PCSK9 activity to reduce LDL levels in order to be able to treat hypercholesterolemia and similar diseases. As will be explained below, the skilled person at that time would not consider as a next step to develop antibodies targeting PCSK9 with a reasonable expectation of success.

Reasonable expectation of success

161. There is no dispute that the skilled person at the priority date was well aware that antibodies are not able to enter the cell and that it would only consider a therapeutic approach based on antibodies targeting PCSK9 if it was established that PCSK9 *in vivo* functions outside the cell (i.e. extracellularly).

162. As discussed in Lagace, previous scientific papers such as Maxwell (see par. @ above) had already shown that PCSK9 played a role in regulating LDLR - and therewith cholesterol - levels and also that PCSK9 functioned intracellularly. Lagace showed the skilled person the existence of the extracellular pathway by which PCSK9 functioned.

163. Contrary to what Respondents have argued and the CDM has considered, apparently proceeding from a wrong interpretation as to the meaning of the implied claim feature of 'therapeutically effective', the mere fact that PCSK9's extracellular pathway *existed* under physiologically relevant conditions, was not sufficient to motivate the skilled person to embark on the project of developing an antibody targeting secreted PCSK9.

164. As explained above, it follows from the implicit requirement that the claimed antibodies must be therapeutically effective that *any* lowering of cholesterol levels did not suffice. The skilled person, when considering an antibody approach, needed a sufficient indication that an antibody approach would cause a noticeable improvement of the medical condition of the patient suffering from hypercholesterolemia and similar diseases, for it to have a reasonable expectation of success.

165. The skilled person would only be motivated to develop antibodies targeting secreted PCSK9 with a reasonable expectation of success if it had a sufficient indication that this would result in a therapeutically effective treatment of hypercholesterolemia and similar diseases, and thus that a sufficiently lower cholesterol level would be achieved by inhibiting PCSK9's extracellular pathway in vivo.

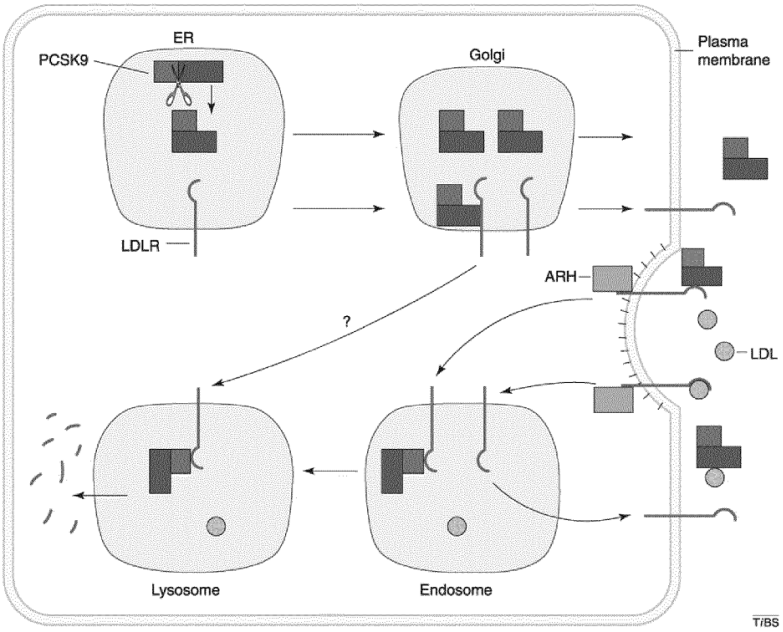
166. Since at the priority date PCSK9 was considered to function by both an intracellular and an extracellular pathways, as also mentioned in Lagace: "*Considered together, the available data now suggest that PCSK9 can function both extra- and intracellularly*", in order to make a reliable prediction whether an antibody approach would be therapeutically effective in vivo, the skilled person needed to know whether the contribution of the extracellular pathway by which PCSK9 functioned would be sufficient to result in such therapeutically effective treatment. The CDM was wrong to consider that the relative contribution of PCSK9's pathways was not relevant to the skilled person.

167. Lagace points out that the relative contribution of the PCSK9 intracellular and extracellular pathways was still uncertain: *"we do not know which pathway predominates under normal and/or pathologic conditions*". The skilled person would understand that Lagace considered further research necessary from the fact that Lagace states *which* experiments are needed to clarify this relative contribution, rather than questioning *whether* such further research would be required.

168. The fact that Lagace observes that the extracellular function of PCSK9 was established at physiologically relevant concentrations of PCSK9, while studies suggesting its intracellular function were performed using PCSK9 overexpression, does not lead to a different conclusion. From the fact that this observation was immediately followed by Lagace's comment on the studies required to determine the relative contribution of extracellular PCSK9, the skilled person would have understood that Lagace did not conclude from this observation that the extracellular pathway was the (most) relevant one, but still considered these studies to be required to clarify the relative contribution of each pathway.

169. The assumption that PCSK9 acted through both the intracellular as well as the extracellular pathway and the importance to establish the relative contribution of these was not only expressed in Lagace, but also in other papers, such as in Fisher 2007 (C7): "*further studies will be required to address the relative roles of PCSK9 in lowering LDLR before or after secretion in vivo*".

170. In the review article of Horton 2007 (C11) in the paragraph with the heading '*Concluding* remarks and future perspectives' it is noted that "*several important mechanistic and clinical questions remain*" and that "*Further studies will be required to identify the specific site(s) <u>in</u> the cell at which PCSK9 functions*." No other conclusion can be drawn from figure 2 of Horton, reproduced below.



171. In the legend to figure 2 in Horton it is stated: "*Current evidence indicates that PCSK9 might work at two cellular sites. The first potential location is in a post-ER compartment, depicted here as the Golgi apparatus, where PCSK9 might target the LDLRs (green) for degradation in an acidic compartment such as the lysosome. In the second possible pathway, the PCSK9 that is secreted binds to LDLRs on the cell surface*." The question mark in figure 2, reproduced above, clearly represents the uncertainty about the precise mechanism of action in the intracellular pathway. The skilled person would not have inferred from that question mark and the lack of a question mark in relation to the extracellular pathway that the extracellular pathway was considered the (more) relevant one. To the contrary, the skilled person would understand from the publication as a whole as well as the legend (with cautious wording like 'might' and 'possible') that much was still uncertain in relation to both mechanisms.

172. Neither would Figure 7 in Qian (C6) "*A working model for PCSK action*", showing the extracellular pathway of PCSK9, lead the skilled person to think that it was the extracellular pathway that was the one relevant in regulating LDLR levels and, as Respondents assert, *"the working model on which drug discovery should be based"*. Since the Qian paper was limited to studies regarding only the extracellular pathway, the skilled person would not draw such a conclusion merely from the absence of a working model showing (also) the intracellular pathway. That is particularly so since it was clear from Lagace and other prior art publications that the relative contribution of both pathways was unknown and Qian did not provide any explanation why the extracellular pathway should be considered the physiologically relevant one. Rather the skilled person would understand that the paper was exploring the not yet fully understood mechanism of (only) the extracellular pathway.

173. Even though inventive step is to be assessed on the basis of the state of the art at the priority date, Amgen rightly pointed out that if something is reported as unknown later, it must have been unknown earlier too. Several papers published after the priority date still mention the unknown relative contribution of PCSK9's extracellular pathway and the relevance thereof for a therapeutical approach using antibodies. In Grefhorst 2008 (D23, p. 1303) it is stated that "*[c]urrently, the relative contribution of the intracellular pathway versus the exogenous pathway of PCSK9-mediated LDLR degradation is not known*." Kwon 2008 (C5, p. 1824) states: "*If PCSK9 functions primarily as a secreted protein in plasma, agents that interfere with the PCSK9:LDLR interaction at the cell surface also have the potential to lower plasma LDL-C levels in individuals with hypercholesterolemia*." Horton 2009 (D30, p. S176) says: "*A third option to inhibit PCSK9 activity is to prevent binding of PCSK9 to LDLRs at the cell surface with small molecules, peptides, or antibodies directed against PCSK9. … The success of this approach depends on PCSK9 functioning primarily at the cell surface*."

174. Finally, the party-experts of both parties in their joint statement agreed "*that the quantitative contributions of extracellular and intracellular to the overall physiological action of PCSK9 were difficult to determine due to limitations in methods such as overexpression which affected both*." (D95 par. 5.2).

175. Respondents' argument that the physiological relevance of the extracellular pathway was recognised while the intracellular pathway was considered to be an artifact of overexpression is thus not supported by its own expert, neither by publications before the priority date.

176. It was not until after the priority date, in April 2009 that McNutt 2009 (D25) provided "*initial evidence that PCSK9 functions predominantly as a secreted factor in mediating cellular LDLR degradation*", which was presented as a new insight: "*The mechanism by which the PCSK9(S127R) protein results in hypercholesterolemia has been suggested to be intracellular (...) The inhibition studies shown in Fig. 5 indicate that PCSK9(S127R) primarily functions extracellularly to degrade the PCSK9-LDLR complex*".

177. At the priority date, the skilled person's understanding from Lagace was still that there was uncertainty about the relative contribution of the extracellular pathway in regulating LDLR levels and thus uncertainty whether an antibody targeting PCSK9 would have the intended therapeutic effect. The skilled person would appreciate that such effect would require sufficient PCSK9 extracellular activity *in vivo*. None of the experiments reported or performed by Lagace established this.

178. The genetic studies described by Cohen and referred to in Lagace, showed the effect of overall lower PCSK9 levels, but did not investigate and could not answer whether PCSK9 functioned inside or outside the cell, or both. Given the uncertainty about the relevance of each of the pathways by which PCSK9 could function, these studies were thus insufficient to reasonably predict the effectiveness of a therapy based on antibodies which relied solely on the extracellular pathway.

179. The in vivo experiment using the parabiosis mouse model in which the circulatory system of a genetically engineered mouse overexpressing PCSK9 is connected to the circulatory system of a normal (wild-type) mouse, demonstrated that extracellular PCSK9 from the genetically engineered mouse caused removal of LDLR in the normal mouse and also increased cholesterol levels in vivo. However, this experiment was carried out with PCSK9 at supraphysiological level (overexpressed PCSK9) leading to a PCSK9 concentration in plasma of the wild-type mice of 17 to 250 µg/ml, compared to a concentration of 0.5 µg/ml in the in vitro experiment at (the upper range of) physiologically relevant level.

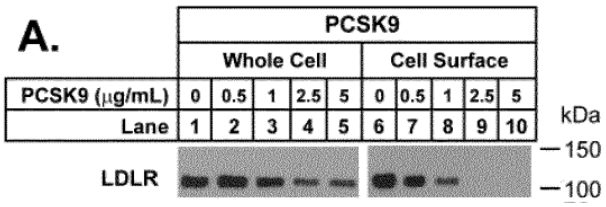
180. In addition to the uncertainty about the relative contribution of the extracellular and intracellular pathway by which PCSK9 functioned to lower LDLR levels, other publications caused the skilled person to doubt whether any relevant binding of PCSK9 to LDLR could take place through the extracellular pathway under physiological conditions (*in vivo*), thus calling into question whether an approach targeting PCSK9 in plasma would be therapeutically effective.

181. Lagace and other publications referring to the Lagace experiments show that relevant scientists in the field considered that the PCSK9 concentration in plasma was the relevant factor for the level of binding to LDLR. In Cunningham (C08) and Fisher (C07) it was reported that the binding affinity of PCSK9 for LDLR is much higher at an acidic pH (inside the cell) than at a neutral pH (outside the cell, in plasma), where it showed a weak binding affinity. Fisher also reported that PCSK9 binding affinity was further reduced by the presence of extracellular LDL particles: "*Together, these results and the in vitro PCSK9- LDLR binding data suggest that LDL exerts an inhibitory effect on the PCSK9-dependent degradation of LDLR by modulating PCSK9-LDLR binding*". Even though Fisher reported that "*complete inhibition of PCSK9 was not achieved even when excess LDL was used (...) suggesting that additional factors such as the local concentrations of PCSK9 and LDL at the cell surface or an accessory cell-surface protein*" to the skilled person the findings in Cunningham and Fisher would still raise doubts whether the required *degree* of PCSK9:LDLR binding would occur in vivo. The skilled person would appreciate that further research with

liver cells in vivo would be required to establish this. Fisher itself reinforces this, where it is stated: "*Although our results show that secreted and internalized PCSK9 can lower LDLR function, further studies will be required to address the relative roles of PCSK9 in lowering LDLR before or after secretion in vivo*".

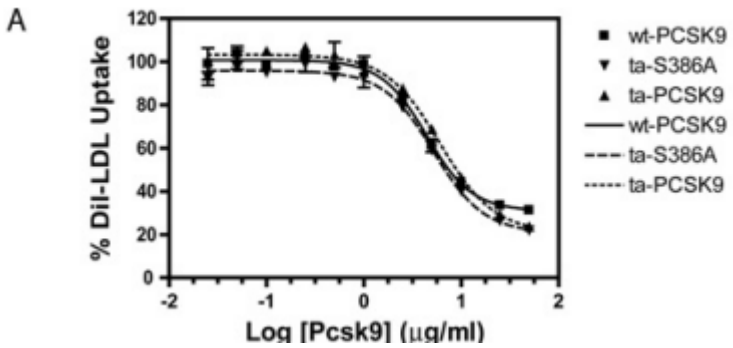
182. The fact that Parker, an inventor himself, in the joint statement speculated that the low binding affinity at neutral pH "*suggested to me that PCSK9 at the hepatocyte surface, and not yet escaped into plasma might exist in such a higher concentration, and at neutral pH might be able to productively bind the LDLR anchored in the membrane*" does not indicate – and Respondents have not substantiated – that the skilled person at the priority date would have the same thoughts. That is particularly so since Lagace, as stated above, suggested that PCSK9 concentration in plasma was considered the relevant factor for PCSK9:LDLR binding. In addition, Parker also stated that he nevertheless thought that antibodies would not be able to productively access PCSK9 and was particularly concerned by the finding that LDL particles themselves were shown to inhibit PCSK9 binding to LDLR extracellularly: "*This effect by LDL in preventing PCSK9 association with LDLR seemed to me a fatal flaw in the arguments that circulating PCSK9 works extracellularly to bind the LDLR*". (D95, par. 5.3-5.5)

183. In addition, experiments reported in other publications also raised concerns whether PCSK9 concentration in plasma would be sufficient to result in a therapeutic effect on LDLR levels *in vivo*. Figure 2 in McNutt (2007, C9) shows "*Catalytically inactive PCSK9 degrades the LDLR when added to HepG2 cells*".



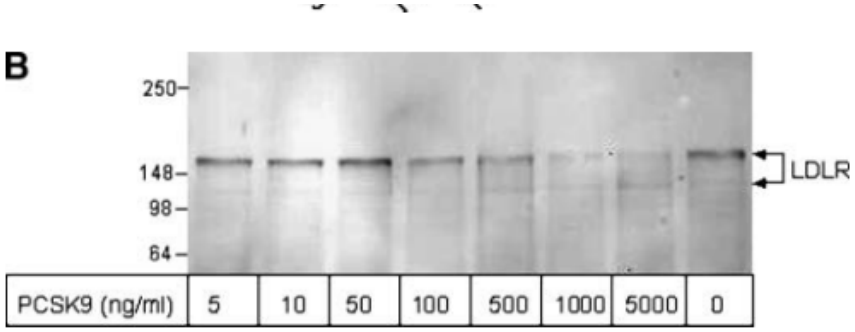
The legend mentions that the "*Relative levels of cell surface LDLR protein were: A, 1.0, 0.9, 0.4, N.D. and N.D. in lanes 6-10 respectively*", thus showing that a PCSK9 concentration of 500 ng/ml in plasma (lane 7) only resulted in a 10% lower LDLR level (0.9 compared to 1.0 without PCSK9), far less than the results reported in Lagace with the same PCSK9 concentration.

184. In Li (C58), Figure 2A shows the effect on LDL uptake by HepG2 cells at increasing PCSK9 concentrations. Even at the higher end (-0.25; $10^{-0.25}$ equals ~560 ng/ml) of the PCSK9 concentration that was considered to be physiologically relevant, there is no, or at best a very marginal difference in LDL-levels. Respondents' argument that this Figure is not representative of LDLR reduction, because it is a different assay measuring LDL-uptake does not hold. The skilled person understands that in the context of this experiment that percentage LDL-uptake is representative of LDLR levels. Reduced LDL uptake into the liver cell (endocytosis) is a direct consequence of the reduction of the amount of available LDL receptors on the cell surface, as the LDL endocytosis is mediated by LDLR (e.g. Horton page 72, left column). Thus, Figure 2A shows that only at supraphysiological concentrations beyond 500 ng/ml, PCSK9 starts to have influence on LDLR degradation and consequently, LDL endocytosis.



185. The results shown in Figure 2A of Li are particularly relevant as, even though a concentration dependent effect is shown, it shows that the effect of PSCK9 on DiL-LDL uptake is not linear but is only clearly visible *as from* the upper limit of the physiologically relevant range of PCSK9 concentration as established by Lagace. Based thereon, it cannot be accepted that the skilled person, when looking at Figure 2 of Lagace, where effects were only measured at PCSK9 concentrations of 500 ng/ml and higher, would have understood that a concentration of less than 500 ng/ml would still have shown an effect on LDLR expression, as Respondents have suggested (par. 4.15 SoR).

186. No clear confirmation that there would be a therapeutically relevant effect on PCSK9:LDLR binding at physiological concentrations can be found in Qian, as argued by Respondents. Respondents have pointed to figure 2B reproduced below.

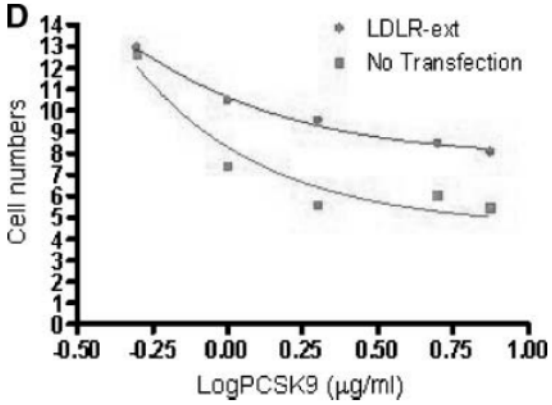


The legend under figure 2B states that it shows concentration-dependent reduction of cellular LDLR in HEK293 cells. The significance of the effects at concentrations of 100 to 500 ng/ml is, however, not clearly apparent, since Qian does not provide any quantification thereof, while the effects are much more distinctive and clearly noticeable at PCSK9 concentrations as from 1000 ng/ml.

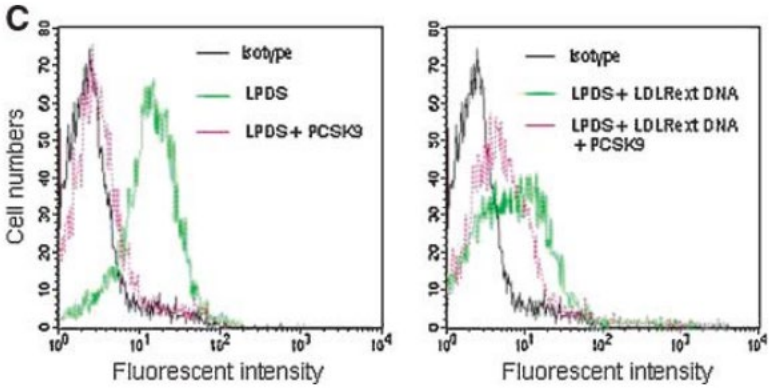
187. The results reported in Figure 3 of Qian, that Respondents also relied on, cannot provide sufficient indication of efficacy at physiological concentration either, since this was performed at a concentration of 3 µg/mouse , from which Respondents' expert Prof. Horton concludes "it is likely that each mouse received a boost of 2 µg/ml PCSK9 to its blood". This is equivalent to four times the physiological level (at the higher end) in human.

188. As Amgen has rightly pointed out, Figure 6D of Qian shown below rather raised serious doubts by the skilled person whether inhibition of PCSK9:LDLR binding by antibodies would be therapeutically effective under physiological conditions (*in vivo*).

189. Figure 6D of Qian, reproduced below, shows results of an experiment wherein LDLR-ext was used as an inhibitor of the PCSK9 interaction with LDLR, thus showing a similar effect as an antibody targeting PCSK9 would have. The Legend mentions that Figure 6D shows "D: Concentration-dependent effects of PCSK9 with or without LDLR extracellular domain overexpression". As can be seen from Figure 6D, the two lines more or less converge at the concentration of 500 ng/ml, the upper end of the physiologically relevant range established in Lagace. At this level, no influence of LDLR-ECD on PCSK9:LDLR binding effect is shown, thus indicating to the skilled person that at this concentration PCSK9 did at best have marginal effect on cell-surface-LDLR. Given the dose-dependent trend shown in Figure 6D, the skilled person would not expect any effect at lower concentrations either, especially in view of Li, where an effect was only visible *as from* the concentration of 500 ng/ml.



190. Respondents without success argued that Figures 6C (shown below) and 6D of Qian if considered together confirm the binding effect of PCSK9 to LDLR at physiological level. According to Respondents, even though both samples in Figure D show comparable cell-surface-LDLR levels at the physiological PCSK9 concentration of 500 ng/ml, the control sample starts with more cell-surface-LDLR - as it submits can be derived from Figure 6C - so it would represent a larger reduction, whereas the LDLR-ECD sample starts with less cell-surface-LDLR, which would represent a smaller reduction.



191. This argument is rejected. Figures 6C and 6D relate to different experiments and there is no indication in Qian they can be combined in the manner Respondents suggest. According to the Legend under Figure 6, Figure 6C shows that "*Cellular overexpression of the LDLR extracellular domain attenuates PCSK9 function*". It is mentioned that "*The left panel shows a marked PCSK9-dependent shift in LDLR-positive cells; in cells overexpressing the LDLR extracellular domain, the PCSK9-dependent shift is attenuated*." It is clear that the results shown in figure 6C relate to the effects of adding PCSK9 at a certain concentration, and as such represent *a* point shown in Figure 6D. It is however not stated at which concentration. The skilled person would appreciate from the results shown in Figure 6C, especially the left panel, that Figure 6C represents measurements at a PCSK9 concentration which has a clear effect on LDLR, and a clear attenuated effect in cells overexpressing the LDLR extracellular domain. Looking at the marginal difference in cell numbers at the PCSK9 concentration of 500 ng/ml with or without LDLR extracellular domain overexpression (where the curves converge) shown in Figure 6D, the skilled person would understand that Figure 6C does not represent the effects of PCSK9 at that concentration, but rather at a higher, supraphysiological, PCSK9 concentration.

192. This interpretation is not contrary to Qian's finding that "*PCSK9 binding to the LDLR extracellular domain is an important step in the process by which PCSK9 acts to downregulate LDLR protein levels*", as Respondents submit. The existence of PCSK9's extracellular pathway indeed follows from Figures 6C and 6D. Importantly, what does not follow – and what would be questioned by the skilled person based on the results – is that this occurs under physiologically relevant PCSK9 concentrations.

193. The lack of a clear effect at physiological level in the experiment shown in Figure 6D was of particular importance to the skilled person, since this is the only experiment before the priority date that shows the effect of *inhibiting* the effect of extracellular PCSK9 on LDLR levels, which mirrors the effect that antibodies are intended to have, i.e. aimed at preventing PCSK9:LDLR binding and increased LDLR levels. The other experiments carried out and discussed in the prior art to the contrary all concerned experiments where PCSK9 was added, resulting in increased PCSK9:LDLR binding and lower LDLR levels, i.e. the reverse from the ultimately envisaged therapeutic effect.

194. The uncertainty about the relevance of the extracellular pathway *in vivo* was also particularly relevant since the skilled person learned from Lagace that the established range from ~50 to ~600 ng/ml PSCK9 in human plasma was based on plasma levels of 72 patients, of which only three had a PCSK9 plasma level of 500 ng/ml or higher while the median level was about 100 - 200 ng/ml. The skilled person appreciated that the PCSK9 concentration of 500 ng/ml used in several experiments, including in Lagace, was at the high end of this range. Although that did not call into question the existence of the extracellular pathway within the established physiological range as such, in order to establish the viability of the antibody approach as an effective therapy, it reinforced the need to determine the relative contribution of the extracellular pathway *in vivo*, as indeed suggested by Lagace.

195. In the review article of Poitier (D26, p. 28862, r.c.) published in 2009, well after the priority date of the patent (among other) Lagace, Qian and Cunningham are discussed. It was observed that "The available compiled data suggest that only supraphysiological levels of circulating PCSK9 have an impact on liver LDLR." Even though this was written after the priority date, Respondents have not argued that or why the skilled person's understanding of these experiments would have been different at the priority date.

196. Respondents without success pointed at the following sentence in Poirier: "*However, because the local concentration of PCSK9 secreted from hepatocytes into the extracellular micro-environment is expected to be much higher than in plasma, PCSK9 may well have an autocrine/paracrine effect in vivo*". Respondents have failed to substantiate that this speculation is based on any data available at the priority date, let alone that this represented common general knowledge of the skilled person at the priority date, quite apart from the fact that at the priority date the skilled person would have understood from Lagace that the PCSK9 concentration in plasma was the relevant factor.

197. Another statement in Poirier, relied on by the Respondents, that "*targeting either pathway, or both, would be an effective method to reduce PCSK9 activity in the treatment of hypercholesterolemia and coronary heart disease*" can equally not be relied on as reflecting the skilled person's perception at the priority date. Amgen has pointed out, and Respondents have not disputed, that Poirier had the benefit of already knowing - based on a recent publication by Amgen scientists (from after the priority date) to which it refers - that a monoclonal antibody (mAb) that neutralizes the interaction of PCSK9 and LDLR is indeed able to reduce the extracellular activity of PCSK9 in vivo. The cited statement can therefore not be considered to reflect the perspective of the skilled person at the priority date. For the same reason, it cannot be relied in support of Respondents' argument that the skilled person would have considered the relative contribution of either pathway to be of relevance, quite apart from the fact that this contradicts Poirier's final statement – in line with other publications at the time - that "*The choice of the best approach to diminish the effect of PCSK9 on LDLR degradation in vivo effectively may be influenced by the relative contribution of both cellular pathways under physiological and pathological condition*".

198. Neither can the statement by the inventor in a post-published patent application (with international publication date 8 September 2008) that "*The secreted form of PCSK9 appears to be the physiologically-active species*", relied on by Respondents and cited in par. 8.50 and 8.59 of the impugned order, be considered to represent the understanding of the skilled person at the priority date. The understanding of an inventor cannot be equated to that of a skilled person and it being post-published, this statement could also not be known to, let alone be common general knowledge of the skilled person at the priority date.

199. In view of all of the above, the skilled person would have understood the statement in Lagace "*If PCSK9 functions as a secreted factor as suggested by the current data, then additional approaches to neutralize its activity, including the development of antibodies to block its interaction with the LDL or inhibitors to block its action in plasma, can be explored for the treatment of hypercholesterolemia*." in context of the publication as a whole, as conditional upon further research confirming that the extracellular pathway *in vivo* was relevant enough for a therapeutically effective treatment based on neutralising secreted PCSK9 activity. There is no reason why the skilled person would have understood Lagace's proposal for additional studies as unconnected to the last paragraph, as suggested by Respondents (par. 3.26 SoR), contrary to their own submission that the skilled person would assess the teaching of Lagace as a whole.

200. The same applies to similar suggestions in Horton and Cunningham. Horton in a paragraph with the heading 'PCSK9 as a therapeutic target' said that "*The low plasma LDL-C levels associated with loss-of-function mutations in PCSK9 indicate that inhibition of PCSK9 either through small molecules, antibodies or RNAi should be effective cholesterol-lowering drugs independently of statins*" (p.75). In the final paragraph of the Cunningham paper it is stated: "*As plasma LDLR binding and receptor-dependent endocytosis is probably the rate-determining step for PCSK9 function, antibodies or small molecules that bind plasma PCSK9 and disrupt its association to LDLR may also be effective inhibitors of PCSK9 function.*"

201. Clearly, the authors had an *effective* therapeutic approach in mind. At the same time, in both papers uncertainties were raised that cast doubt on the effectiveness of such an approach. Horton explicitly mentioned the yet unknown relevance of PCSK9's extracellular pathway in regulating LDLR levels. Cunningham reported to low binding affinity of PCSK9 in plasma and suggested some possible explanations for the low affinity found in *in vitro* experiments: "*The human plasma concentration of PCSK9 is estimated at 1-8 nM*[19]*, suggesting that a small portion of LDLR (1 %-5%) is bound by PCSK9 at plasma pH. It is possible that other plasma factors affect the binding affinity in vivo*" and "*An open question is whether PCSK9 interacts with an unidentified partner to facilitate the release of the prodomain and activate PCSK9 as a protease for LDLR lowering*". Much of this was still uncertain at the priority date.

202. The suggestion and expressed expectation that (among others) antibodies to block PCSK9:LDLR binding as a therapeutic approach would be an effective cholesterol lowering drug for the treatment of hypercholesterolemia and similar diseases would therefore be understood by the skilled person as conditional upon resolving the still existing uncertainties. This is not inconsistent with the conclusions drawn in these papers, as Respondents contend. It is not the existence of the extracellular pathway that was questioned by the skilled person, but rather whether it was sufficiently relevant for an antibody approach to succeed.

203. The conclusion from the above is that at the priority date of the patent, the skilled person could not reasonably predict whether the antibody route would lead to a therapeutically effective treatment of hypercholesterolemia and similar diseases. This prevented the skilled person from having a reasonable expectation of success that an antibody targeting PCSK9 would lead to the solution of the problem he needed to solve. Lagace thus does not contain a sufficiently clear pointer that *would* at the priority date direct the skilled person to develop an antibody as a next step in finding a solution to his problem.

204. It can be left aside whether the skilled person would (only) have had a reasonable expectation of success when there would be a sufficient indication that extracellular pathway was the 'predominant' or 'primary' pathway, as suggested by Amgen and, indeed, expressed in many publications at the priority date and (still) shortly thereafter. The skilled person at any rate required, but failed to have a sufficient indication that the extracellular pathway was sufficiently relevant in vivo (i.e. at physiological level) for an antibody approach to result in a therapeutically effective treatment. That being the case, the question of which percentage of decrease in LDL-C levels would be sufficient for a therapy to be considered effective need not be answered.

205. Respondents' argument, accepted by the CDM, that a skilled person would know how to develop antibodies and would have a reasonable expectation that it would find one within the scope of the claim misses the point. The decisive question here is not whether the skilled person would be able to develop such antibodies without inventive skill being required. That question only comes into play after the skilled person had already decided to develop antibodies as a next step. The relevant question to answer here is, however, the preceding question of *whether*, starting from Lagace, the skilled person *would* consider an antibody approach as a next step with the reasonable expectation that antibodies targeting secreted PCSK9 would have a therapeutic effect on LDLR levels in the first place. This ultimately depends on whether secreted PCSK9 has an effect on LDLR levels to such an extent that neutralising secreted PCSK9 activity would result in a therapeutical effect in vivo (i.e. under physiological conditions). As considered, at the priority date this was still not sufficiently clear. Respondents have – rightly – not argued that this was a problem or open question that the skilled person would have been able to deal with based on its common general knowledge or expertise at the priority date. Therefore, it may be true that at that time the skilled person *could* as a next step have developed antibodies binding to PCSK9 within the scope of the claim with a hope to succeed in finding a therapeutically effective treatment, but it cannot be said the skilled person *would* have done so with a reasonable expectation of success.

206. It is also for this reason that Respondents' argument that before the priority date many pharmaceutical companies were already working on the development of antibodies targeting PCSK9 does not lead to another conclusion. The possible gains of being the first to develop an antibody targeting PCSK9 and the wish to be ahead of competitors in case the extracellular pathway would turn out to be a sufficiently relevant PCSK9 mode of action may have led them to already embark on the project of developing an antibody binding to PCSK9 prior to this being confirmed in the hope to succeed. It does, however, not establish that at the priority date the skilled person had a reasonable expectation of success.

207. To conclude, at the priority date the skilled person starting from Lagace would not develop antibodies targeting PCSK9 as a next step. A combination of Lagace with Zhang (C4) does not alter that. Respondents submit that Zhang teaches how PCSK9 binds to LDLR to have its effects on LDLR and therewith LDL. Zhang does not provide further insight into the relative contribution of the extra-cellular pathway in PCSKs' modes of action. The combination of Lagace with Kwon (C5), also relied on by Respondents, cannot be considered for inventive step evaluation, since Kwon is published after the priority date. The invention must consequently be considered to involve an inventive step.

208. There is no reason to consider any of Amgen's further objections to the CDMS's reasoning in relation to inventive step.

209. The OD also concluded that claim 1 must be considered to involve inventive step, albeit in part based on different considerations.

Conclusion

210. It follows from the considerations above that the appeal is successful and that the impugned decision must be set aside. Respondents' requests to invalidate the patent in its entirety must be rejected.

Costs

211. Respondents are the unsuccessful party and shall in accordance with Art. 69 UPCA bear the costs of the proceedings of Amgen, both at first instance and on appeal.

212. As is clear from the impugned decision and the parties' requests on appeal, the parties agreed that the costs of the proceedings in first instance amounted to EUR 1.375.000 in the revocation proceedings and the same amount in the counterclaim for revocation. In accordance with their requests, the Court of Appeal shall order payment of these amounts by Respondents to Amgen.

213. It is also clear from the parties' requests that an agreement on costs does not exist in relation to the costs on appeal. The Court of Appeal shall order Respondents to bear Amgen's costs of the proceedings. The Court of Appeal determines the value of the proceedings at EUR 100,000,000 per action.

The Court of Appeal:

In UPC_CoA_528/2024 and in UPC_CoA_529/2024

i. sets aside the impugned decision;
ii. rejects the requests to revoke the patent in the Territories;
iii. orders each of Sanofi and Regeneron (separately) to pay to Amgen an amount of EUR 1,375,000 as compensation for the costs of the proceedings at first instance, within 7 days of service of the notice referred to in R. 118.8 RoP;
iv. orders each of Sanofi and Regeneron (separately) to bear the costs of the proceedings on appeal;
v. sets the value of the proceedings at EUR 100,000,000 in each of the UPC_CoA 528/2025 and UPC_CoA 529/2025 appeal proceedings.

Issued on 25 November 2025

Rian Kalden Date: 2025.11.25 09:02:32 +01'00'

Rian Kalden, presiding judge and judge-rapporteur

Patricia Ursula Rombach Digitally signed by Patricia Ursula Rombach Date: 2025.11.25 08:59:15 +01'00'

Patricia Rombach, legally qualified judge

Digitally signed by Åsa Ingeborg Simonsson Date: 2025.11.25 08:52:32 +01'00'

Ingeborg Simonsson, legally qualified judge

Rainer Martin Hermann Friedrich Digital unterschrieben von Rainer Martin Hermann Friedrich Datum: 2025.11.24 21:30:56 +01'00'

Rainer Friedrich, technically qualified judge

Cornelis Schuller Digitally signed by Cornelis Schuller Date: 2025.11.24 21:48:17 +01'00'

Cornelis Schüller, technically qualified judge

SARA MARIA BEIRES MOREIRA DE ALMEIDA Digitally signed by SARA MARIA BEIRES MOREIRA DE ALMEIDA Date: 2025.11.25 09:36:57 +01'00'

Sara Almeida on behalf of the Registry